

THE MACMILLAN COMPANY
NEW YORK · BOSTON · CHICAGO
DALLAS · ATLANTA · SAN FRANCISCO

MACMILLAN AND CO., LIMITED
LONDON · BOMBAY · CALCUTTA
MADRAS · MELBOURNE

THE MACMILLAN COMPANY
OF CANADA, LIMITED
TORONTO

CORNELL CONFERENCES ON THERAPY

VOLUME THREE

Edited by

Harry Gold, M.D., *Managing Editor*

David P. Barr, M.D. McKeen Cattell, M.D.
Eugene F. DuBois, M.D. Walter Modell, M.D.
Ralph R. Tompsett, M.D.

New York
THE MACMILLAN COMPANY
1948

Printed in the United States of America

Set up and electrotyped Published, November, 1948.

MOTTO

It is never too late to give up our prejudices No way of thinking or doing, however ancient, can be trusted without proof

HENRY DAVID THOREAU

Introduction to the Series

The art of treatment represents the merger of two independent bodies of knowledge In their development the two disciplines have followed separate lines at times so far apart that little relationship between them is discernible The science of pharmacology is often and properly concerned with totally impractical matters and a large part of therapeutic knowledge is of necessity an anthology of purely empirical experience

Forces appear to be at work which prevent their free interplay in the face of universal recognition of the fact that the best interests of medical practice are to be served only by their complete integration It is the rare medical curriculum in which pharmacology and therapeutics are so arranged as to weave their teachings into a single and permanent design The courses of pharmacology are isolated in a term or two in advance of the bulk of therapeutics and to a considerable extent, clinicians continue to build the structure of therapeutic teaching with indifferent regard for the base already set for its support.

There is in fact in evidence a degree of competition and distrust between the two Students are informed that thus and so is true in the treatment of the patient in spite of what pharmacology offers to the contrary There is the implication that the one is practical the other theoretical and hence irrelevant This attitude toward the relationship between pharmacology and therapeutics is more apparent in some schools than in others but none is wholly free of it It is of course, unsound for in any system of rational treatment the two

are no more separable than the two faces of the same coin.

In ward and clinic the student is often told to do what in pharmacology he has been taught to avoid, and conversely, in pharmacology he often learns to expect what turns out to be alien to the experience of the clinic It is quite clear that neither has taken full advantage of the opportunities afforded by the other It is also clear that there is urgent need for a forum where pharmacologists and clinicians may come together and talk these things over That, in essence, is the purpose of the Conferences on Therapy

The Cornell Conferences on Therapy were inaugurated in 1937 as a joint venture of the Departments of Medicine and of Pharmacology. Arrangements were made for the participation of every department of the Cornell University Medical College New York Hospital, and the collaboration of other institutions They are scheduled weekly throughout the larger part of the year It is the policy to begin on time and end promptly at the end of an hour.

There is considerable latitude in the conduct of the conferences Certain features characterize the majority of them A group of drugs, a therapeutic procedure, a symptom, or disease is selected as the topic for discussion Practical procedures for the use of the therapeutic measure are outlined by a clinician, and a résume of the experimental basis is presented by some one trained in physiology or pharmacology Approximately half of the period is devoted to informal discussion in which the audience is encouraged to participate.

Free use has been made of the question as a particularly effective device for exciting interest and focusing attention In some conferences the method of the "round table" discussion is employed, the questions being directed to a group of experts on the subject The most successful conferences are among those in which the largest part of the session is devoted to informal discussion through the medium of questions and answers Those, in which sharp differences of views develop and

the evidence is probed, acquire a particularly stirring and stimulating quality Therapeutic prejudice and vague opinion have a somewhat difficult time of it in these conferences

The scope covers the whole range of therapeutics To qualify for a conference, a subject must be a problem in therapy It may be old or new It should be important If there are widely divergent views concerning it, so much the better, since it is the function of the conference to point out how the evidence stands The order of subjects doesn t matter A series of conferences in a particular field has been attempted from time to time, as one series on the treatment of the blood diseases On the whole, it has seemed more practical to avoid the series on one subject, and to take up such topics as seem feasible in relation to their interest at the time and the personnel available to lead the discussion

While the introductory remarks are often prepared, the discussion is for the most part unrehearsed and extemporaneous In many cases the chairman tries to lead the discussion into a planned direction, but frequently the course is determined by the nature of the questions in which the audience appears to show the greatest interest

The conference is no substitute for the formal lecture, the scientific article or the textbook It is not a substitute for any traditional form of medical teaching It does not aim to treat any subject exhaustively, but only to explore some aspects of special interest to analyze the evidence on controversial points of opinion and practice, to elaborate the physiologic and pharmacologic basis of therapeutic measures, and to present these on the level of the general practitioner

There has been a good deal of experimentation in policy and technics Certain features have survived the purpose—to stimulate interest in rational therapy, the method—spontaneous, informal, and free discussion

The conferences were originally designed for the students of the third and fourth year classes of the medical college It

was soon discovered that members of the house staff, of the attending staff, and visiting practitioners had an interest in them. After the first year's experience it seemed that a permanent record would enhance their value. It was anticipated that the reader might consider himself a participant. Accordingly the conferences were taken down by a stenotypist in attendance at each session. The success of the edited record led to the next step, the introduction of the conference to a wider audience through their monthly publication in the *Journal of the American Medical Association* from 1937 to 1940, and since 1940 in the *New York State Journal of Medicine*.

Through their publication it was hoped that they might serve to demonstrate some of the advantages of this method of learning and lead to its adoption by other institutions. It is a method which can be readily adapted to the means and needs of small medical communities and hospital groups.

There has been widespread interest in the monthly publication of these conferences. From the large volume of correspondence and the nature of the comments it has become clear that they are filling a need in medical education. Busy physicians find them a rich source of authoritative information in therapeutics, made more practical by the exchange of views among specialists and general practitioners, made more accessible by the restriction of their scope, and the easy stirring style of the conference method.

In response to numerous requests the final step in their evolution has now been taken, namely, the annual publication of a volume representing a group of conferences selected in the main for their quality and lasting value.

THE EDITORS

Preface to Volume II

During the past year the Cornell Conferences on Therapy have been held regularly and in accordance with the policy and plan outlined in the "Introduction to the Series" They have continued to provide a forum for the informal exchange of views between specialists and general practitioners on problems of treatment Their purpose is to promote the practice of therapeutics based on sound pharmacologic principles

There are signs of an expanding interest in these conferences. Attendance has so enlarged that the former amphitheater could no longer accommodate the audience The sessions are now held in the largest lecture hall of the Medical College *The American Journal of Medicine*, a new monthly publication whose policy it is to make more accessible to the general practitioner the specialized fields of clinical science, expressed an interest in printing the edited record of some of these conferences Accordingly, the monthly publication system has been revised one conference appearing every other month in the *New York State Journal of Medicine* and one every other month in the *American Journal of Medicine* Volume I of the *Cornell Conferences on Therapy* has received a warm reception and about eight months after its publication it was found necessary to prepare for a second printing All of these have encouraged the Editorial Board in the belief that the Cornell Conferences on Therapy are filling an important gap in medical education

Volume II comprises a series of 16 conferences selected from the total of more than 100 which have been published

Acknowledgments

The Editors are indebted to the participants in these conferences not only to those mentioned by name but to the large number of house officers, students, and visiting physicians whose names do not appear in the text. Their impromptu questions and discussions added greatly to the interest and stimulating quality of the conferences. The participation of members of the staffs of the Rockefeller Institute for Medical Research, College of Physicians and Surgeons of Columbia University, New York University College of Medicine, New York Post-Graduate Medical School of Columbia University, and the Sloan-Kettering Institute has been invaluable.

They are indebted to the collaborators who assisted in the editing of the original stenotyped notes, especially to Dr Janet Travell, to Miss Naomi Gold for her aid in the preparation of the final manuscript of Volume III, and to Dr W. Clarke Wescoe for his generous help in the reading of the proof

Grateful acknowledgment is also made to Dr George W Kosmak, Managing Editor of the *New York State Journal of Medicine*, and to Dr Alexander B Gutman, Editor of the *American Journal of Medicine*, for their kind permission to use material which had been published periodically in their respective journals.

List of Conferences

References to conferences (1) Amer J Med 2 296 (Mar) 1947 (2) N Y State J Med 47 2711 (Dec. 15) 1917 (3) Amer J Med 4 130 (Jan) 1918 (4) Amer J Med 3 472 (Oct) 1947 (5) N Y State J Med 47 2111 (Oct 1) 1947 (6) Amer J Med 4 423 (Mar) 1948 (7) Amer J Med 1 93 (July) 1946 (8) N Y State J Med 48 643 (Mar 15) 1918 (9) N Y State J Med 47 1006 (May 1) 1947 (10) N Y State J Med 45 2085 (Oct 1) 1945 (11) Amer J Med 3 231 (Aug) 1947 (12) N Y State J Med 47 1697 (Aug 1) 1947 (13) N Y State J Med 47 387 (Feb 15) 1947 (14) N Y State J Med 47 504 (Mar 1) 1947 (15) N Y State J Med 44 1014 (May 1) 1944

FREDDY HOMBURGER, M D, Research Professor of Medicine, Department of Surgery, Tufts College Medical School

FRANK L. HORSFALL, M D, Member, The Rockefeller Institute for Medical Research, Physician to the Hospital

CHARLES J KENSLER, Ph D, Research Fellow, United States Public Health Service

HERBERT KOTEEN, M D, Instructor in Medicine, Cornell University Medical College, Physician to Out Patients, New York Hospital

NATHANIEL T KWIT, M D, Instructor in Pharmacology, New York University College of Dentistry, Associate Physician, Cardiovascular Research Unit, Beth Israel Hospital Associate Physician (Cardiology), Hospital for Joint Diseases

DANIEL H LABBY, M D, Assistant, The Rockefeller Institute for Medical Research, Assistant Physician to the Hospital

LOUIS LEITER, M D, Clinical Professor of Medicine, College of Physicians and Surgeons Columbia University, Chief, Medical Division, Montefiore Hospital

SAMUEL Z LEVINE, M D, Professor of Pediatrics Cornell University Medical College, Pediatrician in Chief New York Hospital

S S LICHTMAN, M D, Assistant Professor of Clinical Medicine Cornell University Medical College, Assistant Attending Physician, New York Hospital

W S LOEWE, M D, Visiting Professor of Pharmacology, University of Utah

WALSH MCDERMOTT, M D, Associate Professor of Medicine Cornell University Medical College Associate Attending Physician New York Hospital

ALLISTER M MCLELLAN M D, Associate Professor of Clinical Surgery (Urology), Cornell University Medical College,

Associate Attending Surgeon (Urology), New York Hospital, Urologist, New York Hospital, Westchester Division

VICTOR F MARSHALL, M D, Associate Professor of Clinical Surgery (Urology), Cornell University Medical College, Associate Attending Surgeon (Urology), New York Hospital

KIRBY A MARTIN, M D; Instructor in Medicine, Cornell University Medical College, Assistant Attending Physician, New York Hospital

WALTER MODELL, M D, Instructor in Pharmacology, Cornell University Medical College, Associate Physician, Cardiovascular Research Unit, Beth Israel Hospital, Associate Physician (Cardiology), Hospital for Joint Diseases, Physician to Out Patients, New York Hospital

SAMUEL W MOORE, M D, Associate Professor of Clinical Surgery, Cornell University Medical College, Associate Attending Surgeon, New York Hospital, Assistant Visiting Surgeon, Bellevue Hospital

CARL MUSCHENHEIM, M D, Associate Professor of Clinical Medicine, Cornell University Medical College, Associate Attending Physician, New York Hospital

DOUGLASS PALMER M D, Assistant Professor of Clinical Medicine, Cornell University Medical College, Assistant Attending Physician, New York Hospital

HAROLD E. B PARDEE, M D, Associate Professor of Clinical Medicine, Cornell University Medical College, Associate Attending Physician, New York Hospital

FREDERICK S PHILIPS Ph D, Chief, Pharmacology Department, Sloan Kettering Institute.

THOMAS A. C RENNIE, M D Associate Professor of Psychiatry, Cornell University Medical College, Attending Psychiatrist, New York Hospital, Senior Consultant in Psychiatry, Bronx Veterans Administration Hospital; Director, Divi-

The Dose of a Drug

Dr McKeen Cattell In opening the therapy conferences for the current academic year I would like to call your attention to the fact that this represents the tenth year in which these conferences have been conducted As you know they are recorded selected ones are published in the *New York State Journal of Medicine* and now also in the new journal *The American Journal of Medicine* Formerly it was possible for us to supply reprints and these have been quite popular amongst the students and staff of the institution I regret that now however through an arrangement with The Macmillan Company who are publishing an annual volume of Cornell Conferences on Therapy we have agreed to discontinue the distribution of reprints I hope the journals are available to most of you

I would like again to bring up a point which we stress every year namely our wish and our hope that the students will participate fully in the discussions As you know the purpose of these conferences is to provide a medium for informal exchange of views between the various groups who are interested in the problems and we are eager to have the students take part in the questions and comments Often in the warmth of the discussion there has been too much of a tendency to confine it to those in the front rows but it will be our constant endeavor to have all of you participate

The subject of the conference today is The Dose of a Drug We think this is an important topic There are many points of information concerning it which are provided by

experimental pharmacology, and these have not always been fully utilized in drug therapy. The discussion will be opened by Dr. Gold.

Dr. Harry Gold: I am going to deal with a few matters which bear chiefly on problems of dosage. I believe that dosage is one of the very weak spots in drug therapy. A large proportion of the failures in drug therapy results not so much from the choice of the wrong drug, but from the use of the correct drug incorrectly. The fault lies in the dosage. The single dose is either too small or too large, or the dosage plan is, for one reason or another, unsuited for eliciting the full power of the drug for the particular situation. Examples will help to clear the points I wish to make. And right here I should like to state that any resemblance of this to a discussion on cardiology is purely accidental; I shall simply draw on some of the cardiac drugs for purposes of illustration. Whenever I see a patient in heart failure who I judge ought not to be in that state, and who proves the fact by quickly recovering when placed on an appropriate system of treatment, I almost invariably find that the measures which are generally used for the treatment of heart failure have already been applied; a salt-free diet has been prescribed, digitalis has been given, and one or another diuretic has been in use. The failure to achieve satisfactory results was due to improper dosage; the salt intake was not sufficiently restricted, the amount of digitalis may not have been enough, and the system of administration of the diuretics was inadequate for the needs.

A few years ago, we published some studies advocating the use of an "average full dose" of digitoxin to be given at one time for digitalizing patients in heart failure. We encountered many obstacles to the acceptance of this idea. It was argued that the susceptibility of individuals differs; a single average dose will not be enough for the tolerant patients, and will poison the more susceptible ones. You may have seen the paper which appeared August 1945 in the *New York State*

Journal of Medicine, in which the author stated: "It is absurd to speak of digitalizing a patient on 1.25 mg of digitoxin." He then added "There never will be a single dose of digitoxin or any other glycoside which will uniformly digitalize all patients regardless of the age, the sex, the weight, or the general condition" The fact that such a statement was made indicates that some persons apparently believe that such a dose exists, namely, a dose which will digitalize all patients uniformly. Our attention was fixed on this statement by reason of the fact that this heresy was, by implication, ascribed to us. I have heard others voice disappointment with our proposed plan for the use of an "average full digitalizing dose" of digitoxin at one time, because in limited experiences it had failed to produce an expected degree of therapeutic results It soon became clear to us that what troubles most people is the meaning of the term "average dose" We had a conference on digitoxin last year in which considerable time was spent in the endeavor to crystallize the meaning of the term "average dose"

The term "average dose" is very loosely used in therapeutics We discovered, in that discussion, that the term is sometimes applied to the dose which produces the full effect in practically all cases More often, it is applied to the dose which the "average physician" uses without regard for the origin of that usage It is hardly necessary to point out that the average dose and the dose which the average physician prescribes are not the same

In pharmacology, the term "average dose" has a fixed meaning It is the dose which exerts a particular effect in 50 per cent of a population When the end point is a lethal effect, it is referred to as the average lethal dose or the LD_{50}.

The average dose in the pharmacological sense may also be determined in humans, and by substantially similar methods. Again, let us use an example to illustrate the method. If we were to start out to determine the average dose of digitalis which produces a T-wave change in the electrocardiogram, this

is how we might proceed We might start with 100 persons, we might give to each 0 1 Gm digitalis, and 24 hours later we might take an electrocardiogram in order to see what percent age of the subjects showed a change A month later, after the effects of this dose have disappeared, we might give the same group 0 2 Gm digitalis, and again see what percentage showed an effect in the electrocardiogram 24 hours later This pro cedure might be repeated at monthly intervals with increasing doses At the end, we would have certain data, namely, a series of increasing doses and a corresponding series of increasing percentages of responses If we then plot one against the other, we obtain a curve as illustrated in this diagram (Fig 1) It is called a frequency distribution curve This curve provides us with two kinds of information It shows what the average dose is to produce the particular effect, namely, that dose which produces the effect in one half of the population The shape, the steepness, and the length of the curve also show us the range of variability in the sensitiveness of the human popula tion with respect to the particular drug and particular effect.

Such a curve gives us additional information It tells us how useful an average dose for a given drug is likely to be If the curve happens to be a fairly short and steep one, it shows that the sensitivity of one person differs very little from that of another, and that if, in such a case, the average dose were to be given to all, the results would be very satisfactory since some would show the precise therapeutic response, and the re mainder, only a little less or a little more than the exact thera-peutic end point On the other hand, if the curve is fairly long and flat, it shows that the sensitivity of one person differs greatly from that of another, the scatter may be very wide, and the limits so extreme that one patient may require 10 or 20 times as much as another to produce the same effect

If a drug were to show such a long and flat frequency dis tribution curve, the average dose for this drug would not be very useful One would have to start therapy with much less

than the average dose in order to avoid poisoning the more susceptible members of the population.

We have determined the curve for digitalis. It is fairly steep

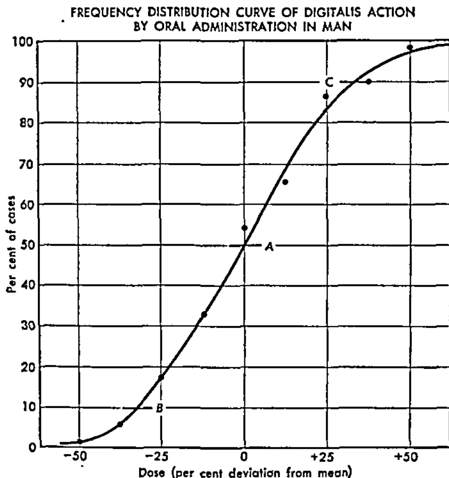


Fig. 1

and short. If 100 persons were to receive the average dose, as you see on the diagram, about 75 of them would show the following results: Some would show exactly the desired response; some, responses to be expected from doses down to 25 per cent less; and some, responses from doses up to 25 per cent more. Almost all are included in the average dose ±50 per

cent Since we know that the end point in digitalization is not very precise, such variations would, for the most part escape detection and even the occasional extremes would not cause serious poisoning In the case of digitoxin, therefore, the aver age full digitalizing dose is a most useful unit of dosage

Well, we know how these matters stand in the case of digi toxin, but for the vast majority of drugs in common use we do not have a frequency distribution curve in humans and we do not know what the average dose is Consider the case of epinephrine for the treatment of an attack of bronchial asthma Where on the curve (see Fig 1) does the usual dose stand? If the usual dose which is employed should happen to stand down at the point B, it would mean that it is too small and that with the usual dose, there may be an unnecessarily large number of failures to produce the effect we are after On the contrary, if the dose which we commonly employ should happen to stand at point C on the curve, it might indicate a dosage level in which we are obtaining an unnecessarily large num ber of cases of poisoning or undesirable side-effects The fact remains that we do not know the average dose of epinephrine Nor do we know the average dose of physostigmine for the treatment of abdominal distention, the average dose of mor phine for pain the average dose of phenobarbital for seda tion, or of castor oil or magnesium sulfate for cathartic action Here is a perfectly simple pharmacological conception which is readily accessible to application in patients but in the clinic we continue to trundle along in the matter of dosage on more or less accidental and empirical experiences So much for the average dose

The next point I should like to discuss is the dosage plan There are essentially two types of dosage plans, one the cumu lative dosage plan, and the other, the non-cumulative dosage plan By the cumulative plan, we mean a plan of dosage which involves giving a small dose at the beginning and repeating at such intervals as to build up a concentration in the blood or

the tissues adequate to produce the therapeutic effects This method is used in the interest of safety If the single full dose is unknown or is dangerous as it is in most cases the full dose is built up by steps each of which by itself causes no harm or no serious toxicity For the ideal system one must know when the peak effect of any dose is reached If the peak is reached in 2 hours after an oral dose let us say the interval between doses should be 2 hours if the peak effect is reached in 6 hours then the interval between the fractions should be 6 hours The use of quinidine is a good example If the objective is to bring to an end an attack of auricular fibrillation or ventricular tachycardia one should start with a small dose say 5 or 10 grains and since it is known that the peak effect is reached in about 2 to 3 hours repeat the dose at these intervals until enough has accumulated to produce the desired effect The total amount of the drug does not matter There can be no talk of failures unless such a cumulative system has been put into operation the end points being the therapeutic results or minor toxic symptoms Picrotoxin in the treatment of barbiturate poisoning is another good example In such a case we often do not know the true depth of the narcosis or the dose of the barbiturate We start with a small intravenous dose which could not do anybody any harm To the peak effect of this which is reached in about 10 or 15 minutes we add the next dose and so we continue by steps until a concentration is reached which begins to produce therapeutic results So much for the cumulative system

The non cumulative plan is just the reverse It involves giving a single effective dose but repeating it at such intervals as will prevent raising the concentration in the blood or the body tissues Here the results may be cumulative but the drug is not The use of the mercurial diuretics is a good example If the loss of weight of the patient with edema is the measure of the therapeutic effect one repeats the dose at such intervals as to produce progressive loss of weight but without significant

increase in the concentration of the mercurial in the bod[y] above that of the first dose. Since these drugs are excreted i[n] about 24 hours, the repetition of the dose at daily interval[s] provides a *suitable non-cumulative* plan.

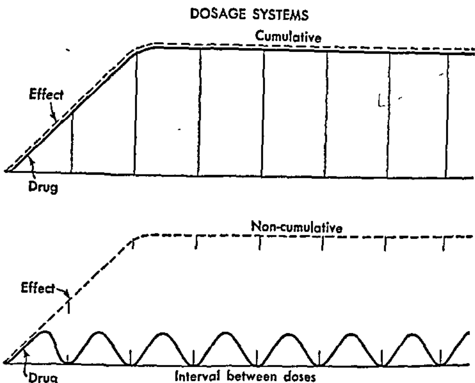


FIG. 2

These diagrams (Fig. 2) illustrate the two systems of dosage which apply to the majority of drugs. One is the system of rising steps, each in itself without danger; and the other is a system of complete curves of absorption and elimination. *As I have indicated, in order to put these mechanisms into most* effective operation, we have to have several bits of information. We should know the approximate speed of absorption of the drug, the time needed to reach a peak effect, and something about the speed of its elimination or duration of action. In this connection, one must remember that cumulation is a

self limiting process for the majority of drugs If one gives a patient a dose of 1 Gm of sodium bromide every day, one finds that the blood concentration of bromide begins to rise, and continues to do so for 2 or 3 weeks The blood concentration curve then levels off even though the same daily dose is continued indefinitely, an equilibrium is reached between the daily dose and daily excretion In the case of digitalis, we see the same phenomenon at work, although we detect it in a different way If a patient with auricular fibrillation and an apex rate of 140 receives 0 2 Gm of digitalis every day, the apex rate begins to slow, it gradually declines to a level of about 70 a minute, below which it may not go even though the same daily dose is continued indefinitely First there was a period of cumulation and then a period when cumulation no longer occurred

The duration of the period of cumulation differs for different drugs In the case of digitalis, a fixed daily dose may show cumulation for 2 to 3 weeks before the effect levels off One cannot be sure that the patient will not become toxic when taking a fixed daily dose, until it has been used for about 3 weeks In the case of quinidine, on the other hand cumulation ceases in about 3 or 4 days If a patient receives, let us say, 1 Gm of quinidine every day, the second day may show greater effects than the first, and the third may show greater effects than the second, but after the fourth day the effects are likely to level off, and no further cumulation occurs after that The period of cumulation is not fixed with precision, but it is of the order of 4 or 5 days for quinidine and of the order of 2 to 3 weeks for digitalis

There is still another point, namely, that the level at which cumulation ceases depends on the size of the daily dose By way of illustration, cumulation of digitalis with a daily dose of 0 1 Gm may level off at an apex rate of 100 a minute, while with a daily dose of 0 2 Gm , at an apex rate of 80 Again, in the case of the bromides cumulation ceases at a lower blood

concentration of bromide when the daily dose is 1 Gm than when it is 2 Gm

There is no doubt that the points which I have discussed as requiring attention in rational systems of dosage play a part in the use of drugs as practiced at the present time I have little doubt that the doses which are prescribed in the case of some drugs are actually the average doses Cumulative and non cumulative systems are at work in dosage plans that are commonly used, but I am inclined to think that their operation is more by accident than design For that reason, we find cumulative systems employed in cases where non cumulative systems would give immeasurably better results and vice versa

To find illustrations, one does not have to go very far It is one of the most common experiences to encounter patients with a particular disorder of rhythm receiving, let us say, 0 3 Gm of quinidine 3 times a day for weeks on end, without any beneficial effects, one could have predicted the failure at the end of the fourth or fifth day Since the system did not provide enough cumulation in the first 4 or 5 days, there remained nothing to do but to raise the single doses or to give fractions at shorter intervals during the day For example, you will find several reports in the literature, pointing to the percentage of cases with auricular fibrillation in which quinidine succeeded in establishing a normal rhythm What meaning have these percentages? If you will examine these reports you will find that a rigid dosage was used for all That is no way to find out how effective quinidine can be

In urgent situations, morphine is often given by hypodermic injection at intervals of 10 or 15 minutes There can be no purpose in choosing such intervals since so little of the first dose is absorbed, its peak effect being reached in a period of 30 to 45 minutes, or in some cases longer I have seen prostigmine used for abdominal distention in doses given at intervals of 6 or more hours The first dose produced no effects, and neither did the others The effects wear off within

about 2 hours Here then is a system of dosage which could by no possibility elicit the therapeutic effects of this drug And when I hear it said that a particular drug was without value in a case in question I ask at once How do you know? Was it used in such a manner as to make sure that the patient could not respond favorably? The textbooks recommend that the mercurial diuretics be given at 4 day intervals The mercurial is excreted within about 24 hours To spread the interval to 4 days simply allows a long period to elapse in which the patient receives no treatment and in this time the condition remains stationary or deteriorates It serves no purpose other than to prolong the period of recovery from the heart failure

Mapharsen in the treatment of syphilis is another case which requires attention from the standpoint of the present discussion A dose is almost completely excreted in 2 to 3 days and while there are some advocates of rapid methods which appear to take this into account the most popular dosage plans call for only 1 injection a week

The cumulative and non cumulative systems of dosage do not exhaust the problems of dosage There are situations in which a more or less fixed plan of dosage needs to be used without adjustments for the needs of the particular individual These are cases in which precise therapeutic end points or minor toxic end points are not available as guides to the adjustment in dosage A good example is the use of digitalis in the heart failure of rheumatic active carditis Here the therapeutic results are often indecisive and if one attempts to increase the concentration by the cumulative method one frequently encounters troublesome and sometimes dangerous toxic symptoms It is therefore best in such a case to adopt a fixed system of dosage with the highest prospects of therapeutic benefits and lowest liability of producing toxic effects and to use that system in all cases without attempting to increase the dose to meet the needs of the particular patient

Therapeutic effects and minor toxic symptoms are the chief

guides to adjustment of dosage in the cumulative systems. There are, however, cases in which special devices are used for that purpose. For example, in the case of insulin in diabetes, the adjustment of dosage depends to a large degree on the amount of sugar which appears in the urine rather than on any specific effects on the patient, although the latter factor is taken into account. Another specific method for adjustment of dosage is shown by the case of Hemophilus influenzae rabbit serum. Here the dosage may be determined by the immune properties developed in the patient's serum or the immunity reaction after an intracutaneous injection of the specific antigen.

I do not believe that we have the time to go into the details of these special problems in this conference.

Dr. Cattell: I would like to make one remark regarding your curve, Dr. Gold, which I think may help to clarify the principle which determines the maximum extent of cumulation over a period of time. A cumulation curve, such as you drew, with a maximum or ceiling effect, represents the cumulation of the effects from the single doses, and is determined by adding the separate curves for each point of time. Thus, one has a whole series of curves of drug effect, and the actual cumulation is measured by the sum of the effect of each of the doses at any point on the time axis. Once the point is reached at which the effect from the first dose disappears, then the added effect will be equal to that which is dissipated, and the curve will level off. So the explanation of cumulation from repeated doses is not obscure, but involves the knowledge of a very simple pharmacologic principle relating to the persistence of the effect of a drug.

Dr. Cary Eggleston: There were two items in Dr. Gold's discussion that I think deserve comment. Dr. Gold discussed the term "average dose." I would like to say a word about that term. In the *United States Pharmacopoeia* the term "average dose" is found in the case of almost every drug. Dr. Gold de-

fined average dose in the pharmacologic sense The Pharmacopoeial definition of average dose is quite another thing, and I think you may be misled if you do not understand the difference between those two uses of that term The *Pharmacopoeia* assigns an average dose on the basis of conference of a considerable group of men supposed to be best informed on the particular agent This dose is merely a rough guide to the practicing physician, so that he will have some idea as to the single dose with which he should start the treatment of the patient. I think that the Pharmacopoeial Committee on Therapeutics realizes that the term "average dose" is misused in fact, I think that they realize that it is an unfair statement, but the physician must have some starting point

Dr Cattell Isn't it usually a minimal dose?

Dr Eggleston It is usually the safe dose par excellence, safe in the sense that it will do no harm It may not be safe because it may be totally inadequate to accomplish the purpose, and by the time one has discovered this it may be too late to remedy the situation The *Pharmacopoeia,* however, cannot deal with all the problems in its statement Keep those two usages separate The Pharmacopoeial average dose is a statement of what is commonly found to be safe and, presumably, what a great many physicians believe is more or less effective when repeated Dr Gold s use of average dose is much more scientific, but unfortunately it has not come into vogue yet except in connection with a few isolated drugs and those drugs are usually ones with more or less simple actions and reasonably clear-cut endpoints for judging their actions

Dr Gold also spoke of the question of cumulation in the use of the mercurial diuretics I don t want to seem to be critical, but I think possibly, there is another idea there which he omitted to mention, namely, that at times we must consider cumulation of effect as well as cumulation of drug We know that the mercurial diuretics available to us today do not remain long within the body Dr Gold has stated the approxi-

mate period as about 24 hours While it is a fact that, within 24 hours, virtually all of the mercurial has been eliminated from the body, it is also true that rapid dehydration is often highly undesirable and at times very uncomfortable for the patient Perhaps, this, rather than the danger of toxicity, is one of the explanations for the frequent use of the mercurial diuretics at longer intervals

Dr Cattell I wonder if we might have a few words from Dr Stewart while we are on this general topic, and then perhaps turn to Dr Gold for a response

Dr Harold J Stewart The diagram that Dr Gold drew, of the T-wave effect and dosage of digitalis, does not seem to me to have a great deal of relevancy to the therapeutic use of digitalis I think almost everybody is agreed that one cannot look at a record of a patient who has had digitalis and tell from the T waves how much digitalis that patient has had From a therapeutic point of view, I think we do not want to give the students the impression that one can look at a record and tell whether a patient is adequately digitalized or not It may be that if one patient were observed, and, allowing time for excretion, were repeatedly digitalized, that patient, on a certain amount of digitalis might exhibit somewhere near the same kind of T wave changes, but one cannot predict what another patient would do with the same or another amount of digitalis in the way of T wave changes Consequently, we cannot use T wave effects as a guide to whether we are getting an adequate thereapeutic effect from digitalis or not

To come back to the word 'average again, it seems too bad that there has seeped into the literature a usage that was not clearly defined in Dr Gold s papers The average dose of digitaline Nativelle, for example, is interpreted by everybody that I have talked to, to mean that dose which will digitalize the patient That is the current notion I think harm to progress in digitalis therapy has been done by the prevalence of this notion As a matter of fact, we see patients now less well dıgı-

talized than 5 or 6 years ago before this notion that one could do it with small amounts I think that in the experience of most people except Dr Gold it takes larger amounts than 1 2 mg to give adequate digitalization In our experience here it is somewhere between 1 8 and 2 mg If 1 2 mg is the average digitalizing dose it is very unusual that we do not see patients in whom this amount achieves digitalization

Dr Cattell I am sure there is no disagreement with what Dr Stewart said with reference to the wide variability among patients in their response to digitalis and the consequent im possibility of using the T wave or any other criterion to estab lish the quantity of digitalis administered It is precisely for this reason that it is so important to have information about in dividual variability in the population to be treated We then have advance information on the probability of the average or any other dose giving the desired therapeutic effect or of its being too large or too small This is a point of great practical importance which has not been given the attention it deserves Thus Dr Gold s average dose of 1 2 mg of digitoxin becomes more informative when at the same time he is able to tell us in what proportion of patients it is ineffective and in what proportion it gives rise to toxic symptoms

Nothing in what I have just said detracts from the evidence obtained by the comparison of the effects of repeated doses in the same patient By such means which eliminate the factor of individual variability it has been established that a defi nite dosage response relationship holds and that the T wave changes correspond quantitatively to the therapeutic actions

Dr Eggleston May I raise a point? I quite agree that the studies by Dr Gold in the attempted establishment of an average dose of digitoxin were exceedingly well planned and very carefully carried out I think the use of the term average dose without specific definition conveys the wrong idea to the practicing physician He certainly generally expects that the dose set by Dr Gold which is quite definitely established

Dr Cattell intimated, if the drug happens to be one in which the therapeutic and toxic effects are close, it may be necessary to start treatment in any particular case with less than the average dose, but if the drug happens to be one in which therapeutic and toxic effects are far apart, treatment may be started in all patients with more than the average dose For example, we might determine the average dose of penicillin which cures pneumonia, but since penicillin is non toxic, it would be desirable to treat all patients not with the average dose, but with a much larger amount, an amount which would cure not 50 per cent of the population, but as close as possible to 100 per cent of the population

As to the specific example of digitoxin, we published a study in which the term "average full dose method of digitalization was used, and the experience was described in which that turned out to be 1 2 mg given at one time Our papers clearly state, and the term "average" clearly implies, that some require more, while others can do with less Dr Stewart appears to be taking issue, and it is not clear to me whether the objection is to the conception of the average dose, or only to the 1 2 mg, or to both

Since Dr Stewart stated that "in the experience of most people, except Dr Gold, it takes larger amounts than 1 2 mg to give adequate digitalization," I should call your attention to the paper by Stroud and Vander Veer in 1937 in which they found that from 1 2 to 2 0 mg of digitoxin was necessary for full digitalization when the drug was given over a period of 5 or 6 days There is also the recent paper by Katz and Wise in the *American Heart Journal* of August, 1945, in which they confirm our results and state that 'digitaline Nativelle in 1 2 mg dosage . . would appear to provide safe, effective, single dose digitalization in undigitalized patients' I believe I know why Dr Stewart is having so much difficulty with the 1 2 mg dose I surmise that he fails to give it at one time, that he does not use the control period which eliminates the effects

of rest in bed as was done in the method by which the 1 2 mg value was established and that his experience may not embrace a sufficient variety of grades of failure from the very mild to the very severe ones Not dealing with an average population he may fail to observe the expected results of an average dose

Dr Eggleston your point about the mercurial diuretics is well taken We all encounter the unpleasant effects of excessive diuresis and in a case in which it has occurred after the first dose we have to wait a few days until the patient recovers However, our solution to the problem is not the one you suggest namely to spread the interval between injections it is rather to keep the interval unchanged but reduce the dose This usually results in a continuous course of improvement or cumulation of effects without the drastic disturbance from excessive single doses given at intervals of 4 days

Dr Eggleston I was not discussing the use of the mercurials I agree with you that often the individual dose should be smaller

Dr Gold I stated at the beginning that any resemblance of this conference to a discussion on cardiology was purely accidental I used the frequency distribution curve which we determined for the effect of digitalis on the T wave of the electrocardiogram as an example of the method which may be used for establishing the average dose of a drug and the range of variability in the response of the human population But since Dr Stewart has broadened the discussion I may state that I agree with him that there is no necessary relationship between the T wave effects of digitalis and its effects in heart failure

Dr Cattell Would you admit that different systems may show different degrees of susceptibility?

Dr Gold Indeed I would In point of fact on the average, it takes about 3 times as much digitalis to bring about the full therapeutic effects in heart failure as to produce changes

Dr Cattell intimated, if the drug happens to be one in which the therapeutic and toxic effects are close, it may be necessary to start treatment in any particular case with less than the average dose, but if the drug happens to be one in which thera peutic and toxic effects are far apart, treatment may be started in all patients with more than the average dose For example, we might determine the average dose of penicillin which cures pneumonia, but since penicillin is non toxic, it would be de sirable to treat all patients not with the average dose but with a much larger amount, an amount which would cure not 50 per cent of the population, but as close as possible to 100 per cent of the population

As to the specific example of digitoxin, we published a study in which the term ' average full dose method of digitalization was used, and the experience was described in which that turned out to be 1 2 mg given at one time Our papers clearly state, and the term 'average' clearly implies, that some re quire more, while others can do with less Dr Stewart appears to be taking issue, and it is not clear to me whether the objec tion is to the conception of the average dose, or only to the 1 2 mg , or to both

Since Dr Stewart stated that "in the experience of most people, except Dr Gold, it takes larger amounts than 1 2 mg to give adequate digitalization," I should call your attention to the paper by Stroud and Vander Veer in 1937 in which they found that from 1 2 to 2 0 mg of digitoxin was necessary for full digitalization when the drug was given over a period of 5 or 6 days There is also the recent paper by Katz and Wise in the *American Heart Journal* of August, 1945, in which they confirm our results and state that digitaline Nativelle in 1 2 mg dosage . . would appear to provide safe, effective, single dose digitalization in undigitalized patients ' I believe I know why Dr Stewart is having so much difficulty with the 1 2 mg dose I surmise that he fails to give it at one time, that he does not use the control period which eliminates the effects

of rest in bed, as was done in the method by which the 1 2 mg value was established, and that his experience may not embrace a sufficient variety of grades of failure, from the very mild to the very severe ones Not dealing with an average population, he may fail to observe the expected results of an average dose

Dr Eggleston your point about the mercurial diuretics is well taken We all encounter the unpleasant effects of excessive diuresis and in a case in which it has occurred after the first dose, we have to wait a few days until the patient recovers However, our solution to the problem is not the one you suggest, namely, to spread the interval between injections, it is rather to keep the interval unchanged but reduce the dose This usually results in a continuous course of improvement or cumulation of effects without the drastic disturbance from excessive single doses given at intervals of 4 days

Dr Eggleston I was not discussing the use of the mercurials I agree with you that often the individual dose should be smaller

Dr Gold I stated at the beginning that any resemblance of this conference to a discussion on cardiology was purely accidental I used the frequency distribution curve, which we determined for the effect of digitalis on the T wave of the electrocardiogram as an example of the method which may be used for establishing the average dose of a drug and the range of variability in the response of the human population But since Dr Stewart has broadened the discussion, I may state that I agree with him that there is no necessary relationship between the T wave effects of digitalis and its effects in heart failure

Dr Cattell Would you admit that different systems may show different degrees of susceptibility?

Dr Gold Indeed I would In point of fact, on the average, it takes about 3 times as much digitalis to bring about the full therapeutic effects in heart failure as to produce changes

vaginal smear which undergoes specific cytological alterations under the influence of estrogens, its end point being a fully cornified smear When one uses this index as a basis for replacement therapy with estrogenic hormones one finds the expected variation in dosage requirements from patient to patient This range of dosage is shown semi diagrammatically in Figure 3 It is, of course, possible to select a range of dosage which will put approximately 50 per cent of patients in full estrus, however, this dose will be excessive for a certain percentage of patients and inadequate for another group This circumstance is completely analogous to the response to the average digitalizing dose of digitoxin which Dr Gold has described

A second variable in the use of the estrogenic hormones is presented by variations in the intervals between injections Thus, you may get entirely different results using any given total dose, depending upon whether the whole amount is given at wide intervals, or daily in divided doses By far the most efficient utilization of the hormone occurs when it is given daily Finally, there is the matter of the cumulative effect of estrogens If a dose is inadequate to achieve a desired effect, it may be given indefinitely without fulfilling its purpose

I am sure that these three examples which illustrate the relevance of Dr Gold s discussion of the fundamental principles which should guide therapy, could be multiplied indefinitely, not only in the field of endocrine therapy, but in virtually all of the medical disciplines

SUMMARY

Dr Gold The discussion in the conference this afternoon centered on problems of dosage The principles were explored and illustrated by examples from a wide variety of drugs There are two systems of dosage by which drugs are administered the cumulative and the non cumulative systems and for their most effective application, use must be made of

then, as to maintaining it It has been my habit to come as close as I can to the dry weight by the use of a regimen not radically different from the one just discussed but there are patients who experience a great deal of discomfort when they are reduced to the dry weight They complain rather bitterly of muscular pains and aches or even of cramps and altogether they are pretty nearly as uncomfortable at times as they were in the milder stages of their congestive heart failure I, therefore, question whether this regimen can be applied as successfully to all patients without considerable individual judgment as to modification from time to time with a little relaxation here, a little change there, in the plan of therapy Of course in essence the plan of therapy is presumptively correct, and I *agree with the general thought behind it*

I would like to ask Dr Gold what average dose of the mercurial he finds necessary, and whether he administers it intramuscularly or intravenously Does he make a choice between the two methods? His initial diet is of course, only a slight modification of the Karell diet, which is essentially a salt free diet It consists of 800 cc of milk per 24 hours Dr Gold raises that to a little higher level of milk and adds 2 quarts of water I think those of you who are not too familiar with the situation should recognize the fact that it is not the water but the sodium in the diet which counts in the retention of fluid in the tissues

I don t think this is the place to quibble over what is the correct therapeutic dose of digitoxin The scheme of 1 2 mg *as the initial dose followed by 0 2 mg daily, works perfectly* satisfactorily in a very large majority of the patients but there are patients small though the numbers may be who will develop signs of digitalis intoxication on this regimen and the dose, therefore, will have to be adjusted to meet their needs You should remember that digitoxin is retained long in the body and continues its action for a long period of time so that while it is the most desirable agent for general therapy in the

digitalis field, you cannot backtrack quite as quickly as you can with some of the more rapidly eliminated glycosides of the digitalis series

Dr Cattell There is one question I would like to ask, Dr Gold, namely, whether you anticipate continuing the mercurial indefinitely in these cases after the congestive failure is relieved

Dr Gold In answer to Dr Cattell, we do anticipate continuing the mercurial indefinitely There are some in whom it may be discontinued after a time There are others who continue to require a daily dose for the remainder of their lives The system provides appropriate means for deciding how long the mercurial will be continued The objective is always kept in mind, namely, to establish the dry weight, and then, to maintain the dry weight After the dry weight has been established by the daily dose of the mercurial, the interval between doses is prolonged In that process of gradually prolonging the interval we discover those cases who do not show a tendency to become ' wet ' even when months or years elapse after the last injection of the mercurial in the same way we also discover those who tend to become wet when the interval is only 24 hours, between these two extremes lie the large numbers of patients in whom the permanent maintenance dose of the mercurial is necessary at any one of a wide variety of intervals, determined for each case individually

In regard to the discomfort resulting from the dry weight, Dr Eggleston, I should mention again our definition of the dry weight ' It is that state in which the optimum amount of extracellular fluid remains in the body Such a state does not produce discomforts Perhaps a more satisfactory term would be optimum weight' rather than dry weight The reason we have avoided the term optimum weight is the fact that it is difficult to define a method for arriving at it When the system is started, the patient begins to lose weight and, after several days to a week or two, in which the mercurial injection

is given daily, the losing of weight comes to a fairly abrupt end This is a sharp end point The vast majority of patients feel at their best when this point is reached a few show undue weakness, muscular cramps, and other unpleasant symptoms which indicate excessive dehydration We allow them to gain a pound or two and they feel better at this higher level We have observed that the production of unpleasant symptoms durii the course of dehydration quite frequently is related to th speed with which it is carried out In general the systen should so be adjusted as to avoid a loss of more than 2 or 3 pounds per day, although I am sure that you have observed many patients in whom a loss of 5 pounds or more per day was tolerated without discomfort It is easy to regulate the speed of dehydration, and thereby control unpleasant reactions by adjusting the daily dose of the mercurial Obviously, the smaller the dose the smaller the diuretic effect

As to your question concerning the dose of the mercurial we usually start with 0 5 cc mercuhydrin If this causes no unpleasant reactions due to allergy or to excessive weight loss and the diuresis is adequate, a weight loss of 2 or 3 pounds we continue that dose daily If the diuresis is inadequate we increase the dose to 1 cc or 2 cc daily in the endeavor to secure a continuous weight loss of 2 or 3 pounds a day In a few cases we have had to increase the dose to 2 cc every 12 hours in order to establish adequate diuresis The system is sufficiently flexible to take care of the major varieties of unusual sensitivity or tolerance to the drug

Our routine plan calls for the intramuscular injection If, for some reason that method is not feasible we give it intravenously It is safer by intramuscular injection

You are quite right in your statement that our diet is essentially a Karell diet Perhaps I should distinguish the important from the unimportant aspects of it It rarely matters whether the patient receives 800 cc of milk or 1,000, or even 1,500 cc a day The point of importance is that such a diet in

sures against the patient receiving more than from 1 to 1 5 Gm salt per day Milk is the simplest form of a light diet to achieve that end, and it makes the least demands on the dietary service of the hospital It is also the least troublesome in the home I should not be so much concerned with the problem of making things easy for those who look after the patient with congestive failure, if it were not for the fact that lapses are so frequent when diets more troublesome to arrange are prescribed The so called low salt diets of hospitals contain from 3 to 6 Gm of salt, and, not infrequently, the saltcellar appears on the tray by mistake Such diets are also relatively inflexible, if the salt content turns out to be too high as seen by the failure of the patient to respond satisfactorily, it is often extremely difficult to have it properly rearranged Of course, if the patient shows some form of intolerance to milk, there is no choice but to arrange a different type of diet containing from 1 to 1 5 Gm of salt We might bear in mind the fact that it is rarely necessary to continue such a low salt diet as is represented by the milk alone for more than about a week, and most patients will co-operate satisfactorily for this relatively brief period of time

Dr Eggleston you stated that you use essentially the same kind of system Do you give the mercurial diuretic every day?

Dr Eggleston I do use the mercurials daily where necessary, and have done so for a considerable time I have never seen any detriment to the patient from their use in this way.

Dr Gold I am glad to hear you say that I would only point out that our system calls for the *routine* use of the daily dose of the mercurial to abolish the attack of congestive failure, rather than in some special cases as implied by your term "where necessary" It is our view that in every case of congestive failure, dehydration is an essential feature of the therapy, and that this should be carried out with the greatest expedition consistent with safety and comfort We have taken the position that, even though complete reversal of the state of con

gestive failure is possible, in many cases with digitalis alone, or with digitalis together with salt restriction and the dose of the mercurial every third or fourth day, it takes unnecessarily long to accomplish the results, and that the daily administration of the mercurial in every one of these cases results in a curtailment of the period of disability Accelerating the speed of recovery without adding discomforts or dangers can be advantageous only

Dr Eggleston May I add that I spoke of the discomfort of the patient during the use of the mercurial for the purpose of making you discuss it a little more, because it is a very real factor and can become very troublesome unless one is cautious in guiding the course of dehydration of the patient

Dr Cattell Dr Stewart, would you care to comment at this point?

Dr Harold J Stewart I think the daily use of the mercurial is about the only thing new in this regimen which Dr Gold has described Everybody, I think, who has been taking care of patients with heart failure, has been weighing them every day, so that is not a new procedure Some have been using small amounts of fluid others large amounts Many have been using milk The only new point is that he advocates the use of daily injections of the mercurial We have not been able to get patients free of heart failure with the use of unlimited amounts of fluid as has been recommended by Schemm We placed a series of patients on an accurately controlled low salt intake and forced fluids, in none were we able to abolish the heart failure, even when we added the mercurials For the most part, I still use limited fluids and a low salt intake

I wonder whether Dr Eggleston s experience with digitoxin has changed since last year I think I remember his saying at a conference last year that he used more than 1 2 mg of digitaline Nativelle to digitalize patients adequately

Dr Eggleston I said that most of the patients required more than that for full digitalization

Dr Stewart In our experience, it has taken from 1 8 to 2 0 mg

Dr Cattell In one dose?

Dr Stewart We gave it to a few patients in a single dose, but we don t advocate that

Dr Cattell Dr Gold, you have had some experience with the single dose of 2 0 mg What happens?

Dr Gold It is much too large for routine single dose digitalization We gave 2 0 mg of digitaline Nativelle at one time to a group of patients and about one third of them developed toxic effects

Dr Cattell Have you any further remarks on Dr Stewart's comments?

Dr Gold I agree with Dr Stewart's view that the individual items involved in our plan of treatment of congestive failure are not new Water, milk, salt restriction, digitalis, mercurial diuretics and weighing of the patient have all been used by others I must confess that I know of no writings other than our own advocating the routine daily dose of the mercurial Dr Stewart regards that as a new feature in our plan, but now I don t believe that even that is new Dr Eggleston just stated that he uses the daily dose of the mercurial at times, and it is probable that others do also I fear, however, that the central theme of my introductory remarks has been overlooked As you know good and bad literature makes use of pretty much the same words the distinction between them lies in the way the words are arranged So it is with our proposed plan for the treatment of congestive failure The secret of its success lies in the way in which the items are put together and carried out Every patient with congestive failure receives 1 to 1 5 liters of milk daily as the sole diet, it is the most certain way of insuring the low intake of 1 to 1 5 Gm of salt Everyone of these patients receives at least 2 liters of water daily (1 glassful every 2 to 3 hours) this is not to elicit a diuretic action of water but to supply the kidney with enough water to enable it to clear

the blood of metabolites produced normally and the excess which comes from the edema fluids The dose of the mercurial is given daily to insure a more or less continuous outflow of edema fluid The patient is weighed daily in order to provide the system of dehydration with a precision control for adjusting the program so as to insure a continuous therapeutic result without the risk of insufficient or excessive effects To keep the patient at the dry weight level by an appropriate adjustment of these factors is the essence of our system of maintenance Most current plans with which patients are provided after leaving the hospital are not systems of maintenance at all, *but retreatments of congestive failure* You will bear in mind that about 20 per cent of cases of congestive failure in the hospital have multiple admissions for the same purpose That is due largely to the fact that the maintenance plans are essentially arbitrary ones, rather than arranged for the individual cases on the principle of reducing the patient to the dry weight, and then maintaining the dry weight by the appropriate adjustment of free water intake, salt restriction, daily digitoxin, and a mercurial injection at an established interval

Dr Stewart stated that everyone weighs his patients with heart failure daily You may be interested in what we found in 502 records of admission for congestive failure in four large hospitals, representing a cross section of current practice in New York City Of these, 51 per cent were not weighed at all, the remaining 49 per cent had an average of one weighing in three days

Not a single case had a chart of the daily weight which is so serviceable in guiding the course of treatment with precision When we charted some of these we found that many patients had been in and out of failure two or three times in the same hospital admission Such a chart has the same value as the fever chart in infections It serves to reveal the adequacy of the system of treatment It also provides a ready means of detecting a complication or a lapse in treatment, otherwise overlooked

These very records were not wanting in chartings of red and blue columns showing fluid intake and output The charting of fluid exchange represents a combination of measures and estimations at best most inaccurate as it is routinely carried out It is a laborious and time consuming nursing procedure which does not yield information worthy of the effort It should be abandoned A simple chart of the daily weight in its place would go a long way in improving the treatment of congestive failure

Dr Walter Modell The Schemm treatment was mentioned in relation to the water intake Is that involved in the system you described?

Dr Gold No it is not Schemm recommended using massive quantities of water forcing fluids 5 or 6 liters or more He used it for its diuretic effect. We don t force fluids in that sense We aim to use only enough water to insure adequate renal function to prevent azotemia and to maintain diuresis induced by salt restriction and the mercurial diuretic We often have a good deal of trouble with the 2 quarts daily It is surprising to see how little water patients will take on their own There is a detail here that is worth mentioning If you prescribe 2 quarts of water and leave it at that just as likely as not you will find that the patient actually consumes only a pint or less The nurse rarely fails to see to it that the patient takes the dose of phenobarbital or cathartic or digitalis but pays little attention to the 2 quarts of water It doesn t seem very important to her In some cases the whole system of treatment breaks down because not enough water is taken I usually order the water as a glassful every 2 to 3 hours and request that the nurse supervise its consumption and chart the amount actually consumed

Dr Janet Travell Is there any objection to getting the patient up and weighing him every day?

Dr Gold We have rarely encountered any trouble The vast majority of patients with congestive failure can be

weighed daily, even those who are very far advanced There are, of course, some cases, such as those with acute coronary thrombosis, who cannot be weighed in the early days This gives me an opportunity to say once again that the daily weighing of the patient is the most important guide in the treatment of congestive failure Without it, the treatment of failure is very much like the treatment of diabetes with insulin and diet without information as to what is going on in the urine with respect to sugar and ketones The patient who is in advanced failure with 50 pounds of edema fluid may show very little symptomatic improvement for several days after the system of treatment is started Very often the physician is discouraged by the apparent absence of improvement and abandons a regimen *which is certain, in the end, to produce satisfactory re*sults If the physician only knew that the patient lost 2 or 3 pounds after the first day of treatment, he could predict a favorable outcome with a fair degree of certainty, no matter how the patient looked or felt at the time This loss of weight in the first day or two provides very useful advance information concerning the outlook If the patient fails to lose weight in the first day or two, it is clear that the regimen is inadequate So often patients linger in bed for several weeks on a system of treatment which yields equivocal results The absence of significant loss of weight in the first two or three days would have provided the indication for prompt intensification of the treatment, and would have avoided the unnecessary prolongation of the period of disability

So, also, in the period of maintenance An abrupt rise in weight indicates that the patient is heading for trouble, usually long before this is revealed by the appearance of symptoms It gives the indication for shortening the interval between the doses of the mercurial or for adjustment in the salt restriction

Dr Cattell Before going on to general questions, perhaps we might hear from Dr Pardee

Dr Harold E B Pardee I think it is not profitable to discuss the question as to whether or not this method of treatment is new I might say that I believe the system as a whole is a new one and that the idea of the daily dose of the mercurials is as far as I know to be credited to Dr Gold It seems to be a very effective measure In considering the daily dose of the mercurial it is well to emphasize the fact that this daily dose is a small one much smaller than we have been accustomed to giving to patients who received the mercurial perhaps twice a week *Another important point which he is again* emphasizing is the use of weight as a guide and I agree heartily with what he said about the records of fluid balance They are a sham and fantasy even with the best nursing care available in the modern hospital In the home it is almost impossible to obtain any information from them that has value The weighing is not difficult You rarely find a patient who is unable to stand on a scale beside the bed This brings us to an other point which has not been discussed namely that many of these patients do better out of bed than in bed They do better sitting in a comfortable chair than they do reclining in bed even in the hospital bed which provides for adequate raising of the head

Another feature which Dr Gold has revived is that of starting off the treatment with milk according to the plan suggested originally by Dr Karell but with modifications This *is a simple way of obtaining a very low salt intake for a short* time I do not think that he would keep this up for a very long period that is not over a matter of 10 days 2 weeks at the outside because these patients need additional food The administration of *digitoxin according to the suggested plan* as Dr Eggleston says usually will prove effective but I am also quite sure that there are some patients who need more If they don t get it in the first 24 hours they should have it in the next. One can often tell by the effect whether or not more digitalis is needed Of course if auricular fibrillation is pres

ing a disturbance in salt and water metabolism leading to tissue hyperhydration, occurring most commonly in chronic heart disease, and resulting usually from a chronic circulatory disorder in the pulmonary or systemic circuit It is most important to bear in mind that increased wetness of the tissues occurs *long before the appearance of the signs which you mentioned* Accordingly, a patient may have congestive failure without pitting of the extremities or enlarged liver, or pulmonary rales, or ascites, or hydrothorax Shortness of breath is an important symptom of congestive failure It may be present without any of the other demonstrable signs of increased wetness of the tissues In fact, in some of the most severe and disabling instances of congestive failure shortness of breath is the only symptom We should remember that interstitial edema of the lungs may not give rise to any rales, yet such patients may be completely incapacitated by dyspnea or orthopnea The system of dehydration which we have outlined provides such patients with complete relief I might call your attention to a most striking case of that kind which we encountered recently The patient had hypertensive and arteriosclerotic heart disease with a massive heart and a gallop rhythm His only complaint was shortness of breath This had progressed to a point at which he was unable to lie down because of the extreme orthopnea and Cheyne Stokes' respiration He had been receiving oxygen, digitalis, intravenous aminophylline, and restricted fluids Since there were none of the frank signs of edema, no rales no enlargement of the liver, and no edema of the legs, *the mercurial diuretics had been withheld* Matters went from bad to worse, and at the time we saw him it looked as if he would hardly survive the night He was promptly placed on the regimen of treatment which we have already outlined, a daily dose of the mercurial, 6 glasses of milk daily as the sole diet, and 3 000 to 4 000 cc of water daily He lost 14 pounds in 4 days and in 7 days was discharged from the hospital almost completely free of symptoms Here was at least

14 pounds of extra fluid which failed to produce any of the standard signs of edema It was found necessary in this case to use a dose of the mercurial every other day for maintenance Several months later, he was still up and about, working and substantially free of symptoms

There are other cases in which the presenting symptom of congestive failure is cardiac pain Some patients who are troubled with the angina decubitus attacks of cardiac pain appearing usually at night awakening them after they have been asleep a few hours are completely relieved by the system of dehydration which we have described This also applies to patients who show none of the standard signs of edema, and are able to carry on fairly active work during the day, but are subject to attacks of pulmonary edema at night The application of the regimen which we have described to establish their dry weight and to maintain the dry weight by suitable adjustment in the regimen renders them free of attacks of pulmonary edema

Dr Steuart In our cardiac clinic we have many patients who come in 1 2 or 3 times a week for their mercurial injections as required for each patient to maintain freedom from heart failure as estimated by the physical signs and change in weight Some of them have been on such a regimen for 7 or 8 years or longer *I had not realized that weighing patients was* not a common practice in taking care of them as it is in our clinic at the New York Hospital

Dr Eggleston I don t think that weighing the patients is a common or a prevalent practice but it is certainly a custom in our clinic and they do very well

I would like to ask Dr *Gold how* much difficulty he encounters in bringing these patients under control when they refuse hospitalization

Dr Gold Sometimes a great deal of difficulty, other times very little This system is perfectly easy to carry out at home A doctor is not needed for the injections Let the patient stay

home and rest in a chair Let him take 4 to 6 glasses of milk daily, and a glass of water every 2 to 3 hours Have a nurse administer the intramuscular injection of the mercurial It might be well to explore the thighs and arms for suitable places for relatively painless injections If a nurse is not available, the patient or a member of the family may be taught to make the injections The problem is similar to that of insulin, and diet in diabetes There the patient is instructed in matters of diet, injections and examination of the urine We would never have achieved the successful treatment of diabetes if a physician or nurse or hospital were necessary for the treatment The same is true of congestive failure The successful control of congestive failure requires that the patient or a member of the family be instructed in the arrangement of low salt diet, in the technic of the mercurial injections and in the keeping of a chart of the daily weight Before that control can be accomplished, physicians must realize the need for educating the patient

Dr Stewart Dr Gold I was not aware that doctors taking care of patients with heart failure did not discuss with the patient or a member of his family how to prepare a salt poor or salt free diet maintenance of body weight etc. This has long been my own practice and the custom in our clinic

Dr Eggleston Dr Gold, do you trust the home scales?

Dr Gold No Have the patient procure a new one The greatest trouble is with the hospital scales They are often inaccurate and inaccessible, and to procure a new one in the hospital is not always so simple a matter

I should like to say a word about a point which Dr Pardee raised namely, the duration of the treatment with the milk diet It is not long In a recent study of ours on 140 admissions for advanced congestive failure the average time from the day of admission to the achievement of the dry weight was approximately 6 days In a series of 502 admissions of similar cases in four large hospitals of New York City, treated by

other methods in current use, the average time required to achieve the same results was approximately 15 days

I may also say a word about Dr Stewart's comment to the effect that it is common practice for the patients in his clinic to receive 1 or 2 injections of the mercurial a week It may be that these patients are doing as well as is possible, but, from the experiences in our clinics with a relatively fixed system of mercurial injections, I would suspect that many of them are being maintained as partial cripples, always on the border of congestive failure, less dyspneic on the first day or two after the injection than on the day before the next injection That is not satisfactory maintenance The best results require an initial period of treatment in which the weight is reduced to *the dry level by the daily dose of the mercurial, in addition to* the other elements of the regimen which we have described, followed by a period of adjustment in the regimen so as to discover the most liberal diet and the longest interval between *injections which suffices to maintain the dry weight The main* tenance plan will differ from case to case, one patient requiring an injection every day, and another being able to maintain a dry weight with an injection once a week, or once in 2 weeks or even longer Of course, this is very difficult to do in the way in which the average outpatient department is operated That is why I urge that the patient be instructed in the technics of this treatment to make him independent of a visit to the clinic for most of the injections Again, the problem of treating congestive failure is essentially the same as that of diabetes

Dr Cattell Dr Leiter of the Montefiore Hospital is here today He has been engaged in the study of the problems of *congestive failure We all would appreciate a few comments* from him

Dr Louis Leiter At the Montefiore Hospital we deal largely with chronic congestive failure I think we all agree that Dr Gold s system is perfectly satisfactory in its general principles

for the management of congestive failure in the acute phase. It is easy to obtain the patient's cooperation at this time. The patient is very ill, he is gasping for breath, and he has little desire for food. Little difficulty is encountered in placing such a patient on a diet of milk. The real difficulty, however, as Dr. Gold and others have intimated, arises when the patient becomes convalescent and faces the problem of continued invalidism in the form of chronic congestive failure. Now the matter of an adequate diet which the patient is willing to continue to take becomes a problem of paramount importance. We question the use of the milk diet by itself at the beginning, because in the next ten or fifteen years of the patient's life, we shall have to be struggling with suitable diets which contain little or no milk. Might it not be wiser to begin treatment with mixed and adequate diets low in sodium, rather than with milk alone? The injection of 3 or more doses of the mercurial a week, furthermore, is a very troublesome business. It is all very well when the physician can go to the patient's home or when a competent nurse can be used for the purpose. It is quite another matter in a large clinic to which patients may have to come in the winter. This involves considerable physical exertion and the difficulty of transportation.

As we looked into the matter, we found that the poor results obtained by patients even in the hands of very competent physicians who made use of digitalis, the mercurials, and other items of treatment were due chiefly to improper diet. The liberal diet seemed to be the chief reason for the frequent readmissions to our hospital. We found that by means of a diet containing only 1 or 1.5 or 2 Gm. of salt, usually less than 1 Gm. of sodium, these patients could be maintained satisfactorily. Most of them reach a point at which they require a mercurial injection only once in 2 to 4 weeks.

The reason for this situation is simple. The patient with congestive heart failure has a glomerular filtration rate well below the normal, but good tubular reabsorption of salt.

Therefore if his diet contains 4 or 5 Gm of salt daily and he excretes only 2 Gm because of his reduced filtration rate it is obvious that he will put on a kilogram of edema fluid every 3 days He therefore would require 1 or 2 mercurial injections a week to be comfortable I should like to place the greatest emphasis on the matter of training patients to use the proper diet Of course there still remain the cases with cardiac cirrhosis and ascites and those with pleural and pericardial effusions who may need more frequent injections of the mercurials or may need to be tapped from time to time There also remain the cases of severe undernutrition which present special problems One of the greatest problems in the management of chronic congestive failure is the prevention of undernutrition I for one, do not believe in allowing a patient a diet fairly liberal in salt and then controlling the congestive failure by several doses of the mercurial a week I do not believe it is a satisfactory means of preventing what eventually will become a state of severe undernutrition We see many patients with congestive failure whose undernutrition as the result of cardiac management is as severe as any encountered in the concentration camps

At this point I would like to ask Dr Gold how he can tell *in connection with the establishment of the dry weight* whether a slow decline in the base line of the weight is due to loss of cellular fluid or to undernutrition

Dr Stewart I wonder if Dr Deitrick is here to say something about the ill effects of the daily dose of the mercurials

Dr Cattell Unfortunately Dr Deitrick *is not here* We were discussing the matter of the dangers of the mercurials yesterday We brought up the attitude of some of the people in New Haven where the mercurials are considered only as a last resort in the treatment of congestive failure on account of the risk of renal injury I am afraid however we will *not have* time for much more general discussion

Dr Nathaniel T Kwit Would Dr Gold comment on the

streptomycin have been most satisfactory in four types of infections first, urinary tract infections caused by Escherichia coli or the other gram negative bacteria which frequently produce infections of the urinary tract such as Bacillus lactis aerogenes, Bacillus proteus, Friedlander's bacillus and, in some instances Bacillus pyocyaneus, second, meningitis caused by Hemophilus influenzae, third, tularemia, fourth, a miscellaneous group of infections, pneumonias, abscesses peritonitis and the like caused by the same group of gram negative bacteria which frequently produce urinary tract infections

Equivocal results have been observed in acute brucellosis and in acute systemic infections caused by the Salmonella group The results in typhoid fever have been disappointing and it is impossible, at this time, to state with any degree of certainty whether streptomycin exerts any effect on the course of the typhoid infection in humans

In the four types of infection in which streptomycin is of unquestioned effectiveness, *the results have generally been as* prompt and, in many instances, as dramatic as we have been accustomed to see following the use of penicillin in pneumo*coccus pneumonia One of the greatest sources of difficulty* in the use of streptomycin is the development by bacteria of resistance to streptomycin This happens with more regularity and greater speed than in the case of other antibacterial agents As a result, the total period during which the drug may be used effectively is limited In the treatment of infections in the urinary tract, in which there is no appreciable degree of anatomic damage or obstruction which cannot be removed the control of the infection by streptomycin may be obtained fairly quickly before the development of bacterial resistance However, if permanent anatomic damage is present so that it is impossible to eradicate the infection completely, the administration of streptomycin may be followed by a remission and, then, by a relapse due to streptomycin *resistant organisms.* The same general principle holds for all types of streptomycin

sensitive infections including tuberculosis Dr Finland has made the interesting observation that, in urinary tract infection, the development of resistance to streptomycin by the gram negative bacilli is appreciably reduced, if not eliminated, by maintaining the urine in a neutral or alkaline state

Streptomycin should be used in the treatment of Hemophilus influenzae meningitis although an alternate type of effective therapy is available In the treatment of Hemophilus influenzae meningitis, it must again be borne in mind that resistance may develop rapidly, and one should be quick to utilize the alternate method of treatment in patients in whom streptomycin does not seem to be effective In Friedlander's pneumonia there is a rapidly necrotizing infection caused by an organism which is susceptible to both streptomycin and the sulfonamides There is theroetical evidence to support the notion that the simultaneous administration of two active drugs might greatly diminish the chance of the development of resistance to either drug Thus it would seem to be wise at this time to use sulfadiazine as well as streptomycin in all of these cases

It may prove worth while to give streptomycin a trial in instances of Salmonella infection in which bacteremia is present, but whether an effect is to be anticipated cannot be said at this time

We may summarize the situation with regard to the nontuberculous infections as follows Streptomycin is a potent agent for the treatment of Escherichia coli infections and it is the only available antimicrobial agent for the treatment of infections due to several other gram negative bacteria It should, *therefore, be used in serious urinary tract infections due to* Escherichia coli, in other types of urinary tract infections caused by Bacillus lactis aerogenes, Bacillus proteus Friedländer's bacillus, and Bacillus pyocyaneus It should also be used in the treatment of peritonitis from appendiceal or diverticular ruptures because this type of peritonitis is fre-

streptomycin have been most satisfactory in four types of infections first, urinary tract infections caused by *Escherichia coli* or the other gram negative bacteria which frequently produce infections of the urinary tract such as Bacillus lactis aerogenes, Bacillus proteus, Friedlander's bacillus and, in some instances Bacillus pyocyaneus second, meningitis caused by Hemophilus influenzae, third, tularemia, fourth, a miscellaneous group of infections, pneumonias, abscesses, peritonitis, and the like caused by the same group of gram negative bacteria which frequently produce urinary tract infections

Equivocal results have been observed in acute brucellosis and in acute systemic infections caused by the Salmonella group The results in typhoid fever have been disappointing and it is impossible, at this time, to state with any degree of certainty whether streptomycin exerts any effect on the course of the typhoid infection in humans

In the four types of infection in which streptomycin is of unquestioned effectiveness, the results have generally been as prompt and, in many instances, as dramatic as we have been accustomed to see following the use of penicillin in pneumococcus pneumonia One of the greatest sources of difficulty in the use of streptomycin is the development by bacteria of resistance to streptomycin This happens with more regularity and greater speed than in the case of other antibacterial agents As a result, the total period during which the drug may be used effectively is limited. In the treatment of infections in the urinary tract, in which there is no appreciable degree of anatomic damage or obstruction which cannot be removed the control of the infection by streptomycin may be obtained fairly quickly before the development of bacterial resistance However, if permanent anatomic damage is present so that it is impossible to eradicate the infection completely, the administration of streptomycin may be followed by a remission and, then, by a relapse due to streptomycin resistant organisms. The same general principle holds for all types of streptomycin

sensitive infections including tuberculosis Dr Finland has made the interesting observation that in urinary tract infection the development of resistance to streptomycin by the gram negative bacilli is appreciably reduced if not eliminated by maintaining the urine in a neutral or alkaline state

Streptomycin should be used in the treatment of Hemophilus influenzae meningitis although an alternate type of effective therapy is available In the treatment of Hemophilus influenzae meningitis it must again be borne in mind that resistance may develop rapidly and one should be quick to utilize the alternate method of treatment in patients in whom streptomycin does not seem to be effective In Friedlander s pneumonia there is a rapidly necrotizing infection caused by an organism which is susceptible to both streptomycin and the sulfonamides There is theroetical evidence to support the notion that the simultaneous administration of two active drugs might greatly diminish the chance of the development of resistance to either drug Thus it would seem to be wise at this time to use sulfadiazine as well as streptomycin in all of these cases

It may prove worth while to give streptomycin a trial in instances of Salmonella infection in which bacteremia is present but whether an effect is to be anticipated cannot be said at this time

We may summarize the situation with regard to the non tuberculous infections as follows Streptomycin is a potent agent for the treatment of Escherichia coli infections and it is the only available antimicrobial agent for the treatment of infections due to several other gram negative bacteria It should therefore be used in serious urinary tract infections due to Escherichia coli in other types of urinary tract infections caused by Bacillus lactis aerogenes Bacillus proteus Friedlander s bacillus and Bacillus pyocyaneus It should also be used in the treatment of peritonitis from appendiceal or diverticular ruptures because this type of peritonitis is fre-

streptomycin have been most satisfactory in four types of infections first, urinary tract infections caused by Escherichia coli or the other gram negative bacteria which frequently produce infections of the urinary tract such as Bacillus lactis aerogenes, Bacillus proteus, Friedlander's bacillus and, in some instances Bacillus pyocyaneus second, meningitis caused by Hemophilus influenzae, third, tularemia, fourth, a miscellaneous group of infections, pneumonias, abscesses, peritonitis, and the like caused by the same group of gram negative bacteria which frequently produce urinary tract infections

Equivocal results have been observed in acute brucellosis and in acute systemic infections caused by the Salmonella group The results in typhoid fever have been disappointing and it is impossible, at this time, to state with any degree of certainty whether streptomycin exerts any effect on the course of the typhoid infection in humans

In the four types of infection in which streptomycin is of unquestioned effectiveness, the results have generally been as prompt and, in many instances, as dramatic as we have been accustomed to see following the use of penicillin in pneumococcus pneumonia One of the greatest sources of difficulty in the use of streptomycin is the development by bacteria of resistance to streptomycin This happens with more regularity and greater speed than in the case of other antibacterial agents As a result, the total period during which the drug may be used effectively is limited In the treatment of infections in the urinary tract, in which there is no appreciable degree of anatomic damage or obstruction which cannot be removed the control of the infection by streptomycin may be obtained fairly quickly before the development of bacterial resistance However, if permanent anatomic damage is present so that it is impossible to eradicate the infection completely, the administration of streptomycin may be followed by a remission and, then, by a relapse due to streptomycin resistant organisms. The same general principle holds for all types of streptomycin

sensitive infections, including tuberculosis. Dr. Finland has made the interesting observation that, in urinary tract infection, the development of resistance to streptomycin by the gram-negative bacilli is appreciably reduced, if not eliminated, by maintaining the urine in a neutral or alkaline state.

Streptomycin should be used in the treatment of Hemophilus influenzae meningitis although an alternate type of effective therapy is available. In the treatment of Hemophilus influenzae meningitis, it must again be borne in mind that resistance may develop rapidly, and one should be quick to utilize the alternate method of treatment in patients in whom streptomycin does not seem to be effective. In Friedländer's pneumonia, there is a rapidly necrotizing infection caused by *an organism which is susceptible to both streptomycin and* the sulfonamides. There is theroetical evidence to support the notion that the simultaneous administration of two active drugs might greatly diminish the chance of the development of resistance to either drug. Thus, it would seem to be wise at this time to use sulfadiazine as well as streptomycin in all of these cases.

It may prove worth while to give streptomycin a trial in instances of Salmonella infection in which bacteremia is present, but whether an effect is to be anticipated cannot be said at this time.

We may summarize the situation with regard to the nontuberculous infections as follows: Streptomycin is a potent agent for the treatment of Escherichia coli infections and it is the only available antimicrobial agent for the treatment of infections due to several other gram-negative bacteria. It should, therefore, be used in serious urinary tract infections due to Escherichia coli, in other types of urinary tract infections caused by Bacillus lactis aerogenes, Bacillus proteus, Friedländer's bacillus, and Bacillus pyocyaneus. It should also be used in the treatment of peritonitis from appendiceal or diverticular ruptures because this type of peritonitis is fre-

streptomycin have been most satisfactory in four types of infections first, urinary tract infections caused by Escherichia coli or the other gram negative bacteria which frequently produce infections of the urinary tract such as Bacillus lactis aerogenes, Bacillus proteus, Friedlander's bacillus and, in some instances, Bacillus pyocyaneus, second, meningitis caused by Hemophilus influenzae, third, tularemia, fourth, a miscellaneous group of infections pneumonias, abscesses peritonitis and the like caused by the same group of gram negative bacteria which frequently produce urinary tract infections

Equivocal results have been observed in acute brucellosis and in acute systemic infections caused by the Salmonella group The results in typhoid fever have been disappointing and it is impossible, at this time, to state with any degree of certainty whether streptomycin exerts any effect on the course of the typhoid infection in humans

In the four types of infection in which streptomycin is of unquestioned effectiveness the results have generally been as prompt and, in many instances, as dramatic as we have been accustomed to see following the use of penicillin in pneumococcus pneumonia One of the greatest sources of difficulty in the use of streptomycin is the development by bacteria of resistance to streptomycin This happens with more regularity and greater speed than in the case of other antibacterial agents As a result, the total period during which the drug may be used effectively is limited In the treatment of infections in the urinary tract, in which there is no appreciable degree of anatomic damage or obstruction which cannot be removed, the control of the infection by streptomycin may be obtained fairly quickly before the development of bacterial resistance However, if permanent anatomic damage is present so that it is impossible to eradicate the infection completely, the administration of streptomycin may be followed by a remission and, then, by a relapse due to streptomycin resistant organisms. The same general principle holds for all types of streptomycin

sensitive infections including tuberculosis Dr Finland has made the interesting observation that in urinary tract infection the development of resistance to streptomycin by the gram negative bacilli is appreciably reduced if not eliminated by maintaining the urine in a neutral or alkaline state

Streptomycin should be used in the treatment of Hemophilus influenzae meningitis although an alternate type of effective therapy is available In the treatment of Hemophilus influenzae meningitis it must again be borne in mind that resistance may develop rapidly and one should be quick to utilize the alternate method of treatment in patients in whom streptomycin does not seem to be effective In Friedlander s pneumonia there is a rapidly necrotizing infection caused by an organism which is susceptible to both streptomycin and the sulfonamides There is theroetical evidence to support the notion that the simultaneous administration of two active drugs might greatly diminish the chance of the development of resistance to either drug Thus it would seem to be wise at this time to use sulfadiazine as well as streptomycin in all of these cases

It may prove worth while to give streptomycin a trial in instances of Salmonella infection in which bacteremia is present but whether an effect is to be anticipated cannot be said at this time

We may summarize the situation with regard to the non tuberculous infections as follows Streptomycin is a potent agent for the treatment of Escherichia coli infections and it is the only available antimicrobial agent for the treatment of infections due to several other gram negative bacteria It should therefore be used in serious urinary tract infections due to Escherichia coli in other types of urinary tract infections caused by Bacillus lactis aerogenes Bacillus proteus Friedlander s bacillus and Bacillus pyocyaneus It should also be used in the treatment of peritonitis from appendiceal or diverticular ruptures because this type of peritonitis is fre

quently caused by *streptomycin sensitive organisms* It is tive, and should be used, in the treatment of Hemop influenzae infections It is as yet of undetermined and p bly questionable value in infections due to Salmonella the Bacillus typhosus

More than a year ago Dr Muschenheim, myself and associates began our studies on the effects of streptomyc human tuberculosis This was prompted by the reports o Hinshaw and Dr Feldman who noted that the administra of streptomycin produced a marked effect on the cour various types of tuberculous infections in man Drs Hin and Feldman were very restrained in the conclusions w they drew from their observations but it was obvious f the data presented by them that their results with tubercu were unprecedented Our own results have constituted a c plete confirmation of their reports

Up until now we have treated about 45 patients with ous types of tuberculosis In general three types of not phenomena were observed in this group of patients First the patients who were acutely ill, there was an abrupt o least, a rapid defervescence with accompanying symptom improvement In some patients the defervescence was as matic as the crisis of pneumococcus pneumonia Second many of the patients there was a marked regression of lesion At times this regression continued to the point of c plete disappearance of the lesions demonstrable by X That specifically has occurred in patients with acute mili tuberculosis The third phenomenon was the developmen bacterial resistance

While the most dramatic results were observed in patie with acute *hematogenous tuberculosis, it is not to be ant* pated that generally favorable results will frequently be tained in this condition There are three reasons for this T first is the high incidence of meningitis as a complication

acute miliary tuberculosis Meningitis may be present either at the start of therapy or make its appearance during the second or third month Secondly, relapsing miliary tuberculosis is to be anticipated, and the third reason is one already indicated for other infections, namely, the development of resistance to streptomycin

In meningitis without miliary tuberculosis the situation is about the same as in the case of miliary tuberculosis I would hazard the guess, on the basis of Dr. Hinshaw s experience, our own experience, the experience in the Veterans Administration program and from the results in a few scattered patients treated here and there, that from one fifth to one tenth of patients with tuberculous meningitis will attain an eventually satisfactory result following the use of streptomycin

Long standing pulmonary tuberculosis, with cavitation and much fibrosis, has not, thus far, been appreciably benefited by the administration of streptomycin The surrounding infiltration may regress The patient may feel better during this phase of the therapy However in every patient thus far, streptomycin resistant strains of organisms have developed.

The form of tuberculosis in which the most satisfactory results have been observed has been the exudative disease of short duration with moderately advanced or even far advanced lesions Here presumably, there are no anatomic barriers to rapid arrest of the lesion In this stage of the disease, effective antimicrobial therapy for 6 or 8 weeks may well spell the difference between success or failure From the studies we have made on the resistance of the tubercle bacilli to streptomycin, it seems that in the majority of patients resistance appears between the fourth and eighth week of therapy Therefore, effective therapy with streptomycin is limited to a great extent to those types of tuberculosis in which it is possible to obtain a significant reversal of the course of the disease within a period of 4 to 8 weeks Exudative disease, with or without thin walled

cavities is the type of pulmonary tuberculosis in which it is conceivable that this could happen, and, from our experience thus far, it seems that it does happen

Just one more point on tuberculosis I think we have clear-cut preliminary evidence that the development of streptomycin resistance by the tubercle bacillus demonstrable *in vitro,* is paralleled by clinical evidence of this resistance *in vivo* Of the first 11 patients who developed bacterial resistance demonstrated *in vitro,* 8 developed clinical relapses during therapy and in 5 of the 8, the relapses progressed to a fatal termination despite the fact that streptomycin therapy was continued In each instance, the relapses occurred after a period of dramatic improvement Therefore, I believe there can be no question but that the development of streptomycin resistance, demonstrable by *in vitro* tests, means that the usefulness of the drug in that particular infection has come to an end I should like to point out that the development of drug resistance by organisms in the central nervous system may however, proceed at an entirely different rate from that in those patients with infections of the lung

Unlike penicillin, streptomycin has important toxic properties Four types of toxic reaction have been observed The first is the so called histamine reaction which does not occur with the presently available material and, therefore, no longer gives any concern

The second type consists of various manifestations of delayed anaphylaxis or sensitivity reactions These reactions are identical with drug fevers and rashes which are observed after the use of any number of drugs When one encounters such a reaction, it is advisable to re evaluate the need for therapy Fortunately, in many cases of non tuberculous infections by the time the reaction appears the need for drug therapy is over and one can discontinue the use of streptomycin without endangering the patient In tuberculosis, on the other hand, that is not the case and in such instances, one must decide

whether the tuberculosis or the sensitivity reaction carries the greater threat to the patient Eosinophilia is another type of sensitivity reaction due to streptomycin The eosinophilia is usually marked and may represent as much as 35 to 40 per cent of the white cell count In one instance in our series, it was accompanied by tenosynovitis No evidence of peripheral vascular disease has been noted thus far although eosinophilia of that degree has caused us some apprehension

The third type of reaction, that of renal irritation, is evidenced largely by granular casts This may be prevented by maintaining an alkaline urine It is difficult to establish whether normal kidneys are permanently damaged by this process I think the evidence is highly suggestive, however, that kidneys previously damaged by other disease can be further damaged by streptomycin Beyond doubt, renal insufficiency appears and progresses during the administration of streptomycin This has now been noted by many observers It is well therefore, to be extremely cautious in the administration of streptomycin to any patient with known renal disease

The fourth type of reaction constitutes the only serious drawback to the use of the drug from the standpoint of toxicity It is a central nervous system reaction characterized by vestibular dysfunction and occasionally accompanied by deafness Evidence of this type of reaction appears in all patients who receive 2 or more Gm of streptomycin daily for longer than 3 or 4 weeks The reaction usually starts as a mild headache which gathers intensity within 24 hours and then disappears The vestibular disorder then appears It is not a true vertigo as a rotary component is lacking There is however a very definite sensation of overshooting the mark for example, in initiating a movement in any direction the patients have the sensation that the movement is continuing after it has actually stopped As a result, they may believe they are falling to one side or the other, or forward, and may be acutely uncomfortable There is considerable variation in the intensity

he ever used it orally in an attempt to sterilize the stools with respect to the typhoid organism?

Dr McDermott We have no experience along those lines We have treated only 6 patients with typhoid fever They were all early cases and were excellent for clinical evaluation since all had bacteremia at the time treatment was started In 4, there was no effect Two patients did very nicely in terms of the progress of their typhoid fever, but we do not know whether the favorable course was related to the streptomycin It would be my guess that streptomycin would have only a temporary effect on the carrier state and that this would not persist after the streptomycin was discontinued

Dr McKeen Cattell I would like to ask Dr McDermott whether we may not anticipate that, if streptomycin is widely used in the treatment of tuberculosis, most infections will eventually be of resistant strains?

Dr McDermott Dr Cattell, *I think we can almost guar* antee it, if enough tuberculosis is treated with streptomycin We do not know, of course, how long the strains remain streptomycin resistant after the drug is discontinued Thus far, the few which we have treated have remained resistant for as long as 90 days following a 4 month period of therapy How ever, it may be that in 6 months or so they revert to their orig inal state of streptomycin sensitivity

I believe, and I am sure Dr Muschenheim agrees with me that the importance of streptomycin in tuberculosis lies not so much in its own potentiality for the cure of tuberculosis as in the demonstration, by means of this drug that it is possible to affect the course of the tuberculous infection with a chemo-therapeutic agent We hope that eventually there will be a better agent than streptomycin for the long pull in this dis ease

Dr Gold Dr McDermott, is there a record of a single pa tient with tuberculosis who has been cured by streptomycin?

Dr McDermott Oh, yes, I would say that of Dr Hinshaw s

patients with meningitis Would you go along with that, Dr. Muschenheim?

Dr Carl Muschenheim Those patients have been observed for 6 months or more, but whether they could be called "cured," I think, is somewhat doubtful I do not think that there has been any more evidence that tuberculosis is "cured" by streptomycin than that it is "cured" by any other method of treatment I am talking about tuberculosis in general I think that we still must speak in terms of "arrest" and that we still must expect relapses caused by the same influences as we have found in the past with other forms of treatment.

Dr McDermott The term "cure" should not be used The action of streptomycin was originally described by Hinshaw and Feldman as "suppressive" Actually, all antimicrobial agents are "suppressive" Streptomycin is in no way different in its effect on tuberculosis than any other antimicrobial agent on other infections What we should anticipate from streptomycin and future antituberculosis agents is not a dissolution of all tubercle bacilli within the body, but rather the conversion of all, or nearly all cases of certain types of active tuberculosis into the equivalent of the best results previously obtained by natural mechanisms

Dr Muschenheim I would like to refer to the statement made by Dr McDermott that streptomycin is not the ideal drug in the treatment of tuberculosis because of the development of resistance I do not think that he intended to convey the impression that streptomycin could not be useful in a general program of treatment of all kinds of tuberculosis He indicated that there are particular phases of tuberculosis, namely, the exudative ones, in which the effect of streptomycin is most dramatic

Another point concerns the fact that the effectiveness in tuberculosis may be of brief duration Therefore, in applying streptomycin in association with other forms of treatment, such as surgery or collapse therapy of various kinds, we should

choose the time very carefully We do not want to shoot our bolt, so to speak, before we really need it

Dr Walter Modell This is the first time, I think, that I have heard Dr McDermott advise the combined use of two chemotherapeutic agents I wonder, in view of that, what he thinks about using streptomycin together with one of the sul phones such as promin, which was recommended some time ago as an effective antitubercular agent

Dr McDermott Implied in your query is the view that the combined use of antimicrobial agents may materially diminish the development of resistance to either agent There is impres sive *in vitro* evidence that it may be so This has been a subject of a great deal of debate and speculation

The combined use of streptomycin and promin is now be ing tried out It should take a relatively short period of time to find out whether promin is useful when combined with streptomycin, because the development of resistance to strep tomycin is so uniform

Dr Morris Pearlmutter How should one treat a fulmi nating case of influenzal meningitis, Dr McDermott?

Dr McDermott I am probably not the one best qualified to answer that since I am not a pediatrician, but I will try my hand at it I would use streptomycin alone for a 24 hour pe riod At the end of that time, I would be guided principally by the findings in the spinal fluid, especially by the number of bacteria This is relatively easy to demonstrate by the quellung test If it falls from 1,000 to the order of about 20, I would continue the streptomycin but if the effects are not as impressive, I would most certainly switch to Dr Alexander s immune serum and sulfadiazine In the few patients whom we have treated, the results have been dramatic with streptomycin alone

Dr Pearlmutter Suppose the count dropped but slightly, would you then be inclined to treat the patient with all three agents?

Dr McDermott I would certainly see no objection to treating with all three or with a combination of two Sulfadiazine presents no problems Immune serum is rather expensive and so is streptomycin I see no theroetical objection, however, to using all three agents together

Dr Gold Dr Levine, could we have an expression of opinion from you?

Dr Samuel Z Levine In a particularly fulminating case of influenzal meningitis on the basis of Dr Alexander s experience it would seem wise not to postpone the use of the three agents in combination if the response to streptomycin alone were not dramatic. As Dr McDermott pointed out it cannot do any harm except for the cost, and it may do a lot of good

Dr McDermott I did not see Dr Levine there or I would not have been so presumptuous as to answer that question

Dr Gold Tell us something about the cost

Dr McDermott As a matter of fact, in influenzal meningitis, the expense of streptomycin is not so great, because one is usually dealing with an infant or small child One half to 1 Gm depending upon the size of the child, is usually enough for a daily dose The market price fluctuates but streptomycin is purchasable at this time for approximately $4 00 for 1 Gm

Visitor What has been the experience with the so-called minimal lesions in tuberculosis?

Dr Muschenheim We have not treated minimal lesions although we had one case which was virtually minimal It was moderately advanced because there was a very tiny cavity This promptly closed with streptomycin The patient was a young colored girl who, with a good deal of bed rest, had failed to obtain an arrest of the disease It was only because the disease has such a serious prognosis in her particular age, sex, and race that we even considered treating her with streptomycin

In general, I believe, and I think Dr McDermott agrees with me, that minimal cases should not be treated with streptomycin We know nothing yet about the late toxic sequelae

of the drug Dr McDermott has called attention to the eosinophilia which causes some concern since it may indicate serious late sequellae We hesitate to give streptomycin in these minimal cases because we are afraid of causing serious toxic effects in the treatment of a disease which has an almost uniformly favorable prognosis when treated by methods known to be safe

Visitor If the organism becomes streptomycin resistant, is the infection any more dangerous?

Dr McDermott That is a problem which has concerned us and about which there is no information It certainly should be investigated We must find out whether the continued administration of streptomycin after development of streptomycin resistance produces a more fulminating type of infection

Dr Gold How do you view the mechanism of the very rapid development of resistance to streptomycin in view of the more or less generally accepted idea that the development of resistance is due to the breeding out of resistant strains? Why does that happen so quickly in the case of streptomycin and relatively slowly in the case of penicillin? It is fundamentally the same type of process, breeding out the tolerant or resistant members of a strain

Dr McDermott I think that the development of bacterial resistance proceeds by several mechanisms, breeding out is only one, mutation is another There is evidence that adaptive enzymes can be developed by bacteria The selective breeding of mutants is generally believed to be the most reasonable explanation for most instances of the recognized resistances Most organisms against which penicillin is effective show remarkable uniformity in their sensitivity *in vitro* among the individual members of a species There are some exceptions such as the staphylococcus It seems to be otherwise for streptomycin The Escherichia coli against which streptomycin is so effective, for example, shows rather wide differences in the sus

ceptibility of members of a species. A fundamental difference in the point of attack on the vital functions of the bacterial cells in the case of the two drugs may be one factor in explaining the ease with which streptomycin produces bacterial resistance. This applies to the mechanism of breeding out resistant members as well as to any other mechanisms by which resistance within bacterial cells may be developed.

Intern: I would like to ask if the kidney damage caused by streptomycin is permanent or reversible?

Dr. McDermott: Some of it is certainly reversible. We had one patient, about 30 years old, who, in the course of a very serious tuberculous pneumonia, developed evidence of fairly marked renal damage during a 60-day period of streptomycin therapy. The urea clearance fell to about 40 per cent of normal. During the second 60-day period of treatment, the renal damage subsided concurrently with the improvement in the tuberculous pneumonia. Another patient, who had only one kidney, suffered renal damage during the first course of treatment with streptomycin. A second course of treatment for 90 days, however, produced no further apparent damage, the blood urea nitrogen remaining somewhat above 30 mg. and the urea clearance below 20 per cent of normal.

Dr. Cattell: I would like to ask Dr. McDermott if he has tested the resistance of the organisms in the tuberculous patients before using streptomycin?

Dr. McDermott: We have in every case, and all of them were sensitive. This was also the case with the organisms which were tested by Dr. Youmans in Dr. Hinshaw's studies. I must emphasize that the conditions of the test are not such as to give one a wide sampling of the individual cells in a particular culture. No one has as yet carried out the necessary test of streaking out the culture and testing a number of different cells for sensitivity.

Dr. Gold: Do not all routine *in vitro* tests for sensitivity suffer from the same defect, namely, that they fail to separate

out resistant from sensitive members in the sample which is being tested?

Dr. McDermott: That is so, Dr. Gold, when the test is performed in liquid media. It is not so when the organisms are plated out. That is what is being done in the case of the staphylococcus, for example.

Intern: I would like to ask if streptomycin has an effect on the hematopoietic system. I remember one patient in whom the platelet count dropped from 350,000 to around 40,000 after streptomycin administration. When the streptomycin was discontinued, the platelet count returned to normal.

Dr. McDermott: Was there any bleeding?

Same Intern: Yes, there was bleeding when the count was at the low point. The bleeding was the reason for the count. This patient had had typhoid fever and the gall bladder was removed because he was a typhoid carrier. He then developed a typhoid abscess in the operative wound, for which the streptomycin was given.

Dr. McDermott: Was he receiving a sulfonamide?

Same Intern: No.

Dr. McDermott: Such a reaction might be expected after a sulfonamide, but I have never encountered it after streptomycin. There is a report of a patient with acute brucellosis treated with streptomycin who developed thrombocytopenic purpura from which he recovered completely. We have seen leukopenia and, in one case, it was associated with granulocytopenia. We have seen these reactions in patients with acute miliary tuberculosis in whom the possibility of bone marrow involvement was also present.

Dr. Muschenheim: Dr. Bunn told me of a patient with miliary tuberculosis who developed granulocytopenia which improved after the discontinuation of streptomycin. This seemed to rule out bone marrow infection due to tuberculosis.

Dr. Gold: Dr. McDermott, will you say something about the dosage and the preparations?

Dr. McDermott By great good fortune, the original unit of streptomycin coincided with 1 0 microgram of the active sub stance This makes it convenient, therefore, to express dosage in terms of weight of the drug

Dr. Gold Are doses expressed in terms of the pure crystalline substance?

Dr McDermott Yes, in terms of the pure streptomycin base. The material which is marketed is in the form of the hydrochloride or the sulfate, and it is not pure The label on the vial indicates the amount of the pure base to which the contents of the vial is equivalent Thus in a vial labeled as equivalent in activity to 1 Gm of streptomycin base, the actual weight of the material in the vial may be greater than 1 Gm. because of the impurities Because of the differences in the amount of impurities in different preparations, two vials labeled 1 Gm streptomycin may contain different amounts of material while both represent the activity of the same amounts of pure streptomycin

The material is soluble in water It can be administered dissolved in distilled water It is usually given by intramuscular injection

For most infections, 1 to 3 Gm daily is adequate In tuberculosis, Dr Hinshaw s group first used 1 Gm and then 1 5 Gm. We used 3 Gm from the beginning There is no evidence that our patients have done any better than Dr Hinshaw's There is no evidence that large initial doses prevent the development of bacterial resistance, at least bacterial resistance has not been prevented by even such large doses of streptomycin as cause toxic effects For most urinary tract infections, I think 1 Gm. per day should be sufficient In Hemophilus influenzae meningitis the dose depends on the size of the child I think 0 1 Gm is the upper limit of safe dosage in an adult when the drug is administered by the intrathecal route Larger doses than that are sometimes tolerated but are sometimes associated with toxicity. We would, therefore, advise using single doses of

streptomycin no larger than 0.1 Gm. when given by the intrathecal route.

Dr. Gold: Do you prefer the interrupted intramuscular method of administration?

Dr. McDermott: Usually I do. In a non-fulminating infection, I would say that therapy during 18 of the 24 hours would be adequate. In a fulminating infection, such as Hemophilus influenzae meningitis, injections should be given at 3-hour intervals around the clock.

Dr. Gold: Not by intravenous injection?

Dr. McDermott: It is unnecessary.

Dr. Janet Travell: Does the material cause pain?

Dr. McDermott: Yes, the commercially available material of the past two years was painful to a variable degree. Highly purified crystalline material, at least 95 per cent pure, such as we used in the tuberculosis study, is no more painful than the best penicillin preparations.

Dr. Gold: Is there any material on the market that is as pure as the standard against which the streptomycin of commerce is compared in the assay?

Dr. McDermott: No, but I believe that the large manufacturers are soon going to have on the market material of about the same grade of purity as the highly purified material which we used.

Dr. Travell: Will that increase the cost?

Dr. McDermott: It increases the cost to the manufacturers considerably because they lose about 50 per cent of the yield in the crystallization. I doubt that it will materially increase the cost to the public in a competitive market if there is enough demand for it.

Dr. Pearlmutter: Has streptomycin been given a trial in virus pneumonia?

Dr. McDermott: I do not know of any instances in which it has, but I assume that it has. I would certainly be opposed to using it in atypical pneumonia. Although the drug is rela-

tively non toxic in comparison to some drugs, it is not innocuous and not to be used for self limited, benign infections

Dr Gold How does the problem of oral administration stand at the moment? Animal experiments show that it is absorbed by the oral route and that the fatal dose by mouth in mice is just about 3 times that by subcutaneous injection I am wondering whether the situation here is analogous to the case of penicillin in which, if we give something like 5 to 10 times the parenteral dose, we may obtain perfectly satisfactory effects by the oral route Have you any opinion about that?

Dr McDermott We have not pursued the subject because of the scarcity of the material

Visitor At Bellevue Hospital a series of typhoid carriers was examined First the drug was given intravenously There was no conspicuous effect on the typhoid organism There was a high incidence of renal toxicity among these patients Then, some of them were given the drug orally There was apparently less renal irritation For a time the stool cultures were negative but subsequently reverted to positive I am not certain of the range of dosage when it was given orally, I think it was of the order of twice the intravenous dose

Another Visitor Is it possible to inject streptomycin intramuscularly in wax and oil to avoid multiple injections as is now often done with penicillin?

Dr McDermott Unfortunately that is not practicable because the amount of the drug which would be given in such a fashion would be too large, much greater than that in the case of penicillin

Intern At a recent therapy conference on urinary tract infections *we were left with the impression that the sulfa drugs* are far more useful in these infections than streptomycin I wonder if you share those sentiments?

Dr McDermott In uncomplicated infection by Escherichia coli which is the most common infection of the urinary tract seen by the internist and the obstetrician I believe that sul

streptomycin no larger than 0 1 Gm when given by the intra thecal route

Dr Gold Do you prefer the interrupted intramuscular method of administration?

Dr McDermott *Usually I do* In a non fulminating infection, I would say that therapy during 18 of the 24 hours would be adequate In a fulminating infection, such as Hemophilus influenzae meningitis, injections should be given at 3 hour in*tervals around the clock*

Dr Gold Not by intravenous injection?

Dr McDermott It is unnecessary

Dr Janet Travell Does the material cause pain?

Dr McDermott Yes, the commercially available material of the past two years was painful to a variable degree Highly purified crystalline material, at least 95 per cent pure, such as we used in the tuberculosis study, is no more painful than the best penicillin preparations

Dr Gold Is there any material on the market that is as pure as the standard against which the streptomycin of commerce is compared in the assay?

Dr McDermott No *but I believe that the large manufac*turers are soon going to have on the market material of about the same grade of purity as the highly purified material which we used

Dr Travell *Will that increase the cost?*

Dr McDermott It increases the cost to the manufacturers considerably because they lose about 50 per cent of the yield in the crystallization I doubt that it will materially increase *the cost to the public in a competitive* market if there is enough demand for it

Dr Pearlmutter Has streptomycin been given a trial in virus pneumonia?

Dr McDermott I do not know of any instances in which it has but I assume that it has I would certainly be opposed to using it in atypical pneumonia Although the drug is rela

tively non toxic in comparison to some drugs, it is not innocuous and not to be used for self limited, benign infections

Dr Gold How does the problem of oral administration stand at the moment? Animal experiments show that it is ab sorbed by the oral route and that the fatal dose by mouth in mice is just about 3 times that by subcutaneous injection I am wondering whether the situation here is analogous to the case of penicillin in which, if we give something like 5 to 10 times the parenteral dose, we may obtain perfectly satisfactory effects by the oral route Have you any opinion about that?

Dr McDermott We have not pursued the subject because of the scarcity of the material

Visitor At Bellevue Hospital a series of typhoid carriers was examined First the drug was given intravenously There was no conspicuous effect on the typhoid organism There was a high incidence of renal toxicity among these patients Then, some of them were given the drug orally There was apparently less renal irritation For a time the stool cultures were negative but subsequently reverted to positive I am not certain of the range of dosage when it was given orally, I think it was of the order of twice the intravenous dose

Another Visitor Is it possible to inject streptomycin intramuscularly in wax and oil to avoid multiple injections as is now often done with penicillin?

Dr McDermott Unfortunately, that is not practicable because the amount of the drug which would be given in such a fashion would be too large, much greater than that in the case of penicillin

Intern At a recent therapy conference on urinary tract infections we were left with the impression that the sulfa drugs are far more useful in these infections than streptomycin I wonder if you share those sentiments?

Dr McDermott In uncomplicated infection by Escherichia coli which is the most common infection of the urinary tract seen by the internist and the obstetrician I believe that sul

streptomycin no larger than 0 1 Gm when given by the intra thecal route

Dr Gold Do you prefer the interrupted intramuscular method of administration?

Dr McDermott Usually I do In a non fulminating infec tion, I would say that therapy during 18 of the 24 hours would be adequate In a fulminating infection, such as Hemophilus influenzae meningitis injections should be given at 3 hour in tervals around the clock

Dr Gold Not by intravenous injection?

Dr McDermott It is unnecessary

Dr Janet Travell Does the material cause pain?

Dr McDermott Yes, the commercially available material of the past two years was painful to a variable degree Highly purified crystalline material, at least 95 per cent pure, such as we used in the tuberculosis study, is no more painful than the best penicillin preparations

Dr Gold Is there any material on the market that is as pure as the standard against which the streptomycin of commerce is compared in the assay?

Dr McDermott No, but I believe that the large manufac turers are soon going to have on the market material of about the same grade of purity as the highly purified material which we used

Dr Travell Will that increase the cost?

Dr McDermott It increases the cost to the manufacturers considerably because they lose about 50 per cent of the yield in the crystallization I doubt that it will materially increase the cost to the public in a competitive market if there is enough demand for it

Dr Pearlmutter Has streptomycin been given a trial in virus pneumonia?

Dr McDermott I do not know of any instances in which it has but I assume that it has I would certainly be opposed to using it in atypical pneumonia Although the drug is rela

tively non toxic in comparison to some drugs it is not innocuous and not to be used for self limited, benign infections

Dr Gold How does the problem of oral administration stand at the moment? Animal experiments show that it is absorbed by the oral route and that the fatal dose by mouth in mice is just about 3 times that by subcutaneous injection I am wondering whether the situation here is analogous to the case of penicillin in which, if we give something like 5 to 10 times the parenteral dose, we may obtain perfectly satisfactory effects by the oral route Have you any opinion about that?

Dr McDermott We have not pursued the subject because of the scarcity of the material

Visitor At Bellevue Hospital a series of typhoid carriers was examined First, the drug was given intravenously There was no conspicuous effect on the typhoid organism There was a high incidence of renal toxicity among these patients Then, some of them were given the drug orally There was apparently less renal irritation For a time the stool cultures were negative but subsequently reverted to positive I am not certain of the range of dosage when it was given orally, I think it was of the order of twice the intravenous dose

Another Visitor Is it possible to inject streptomycin intramuscularly in wax and oil to avoid multiple injections as is now often done with penicillin?

Dr McDermott Unfortunately, that is not practicable because the amount of the drug which would be given in such a fashion would be too large, much greater than that in the case of penicillin

Intern At a recent therapy conference on urinary tract infections we were left with the impression that the sulfa drugs are far more useful in these infections than streptomycin I wonder if you share those sentiments?

Dr McDermott In uncomplicated infection by Escherichia coli, which is the most common infection of the urinary tract seen by the internist and the obstetrician I believe that sul

streptomycin no larger than 0 1 Gm when given by the intra thecal route

Dr Gold Do you prefer the interrupted intramuscular method of administration?

Dr McDermott Usually I do In a non fulminating infec tion, I would say that therapy during 18 of the 24 hours would be adequate In a fulminating infection such as Hemophilus influenzae meningitis injections should be given at 3 hour in tervals around the clock

Dr Gold Not by intravenous injection?

Dr McDermott It is unnecessary

Dr Janet Travell Does the material cause pain?

Dr McDermott Yes, the commercially available material of the past two years was painful to a variable degree Highly purified crystalline material, at least 95 per cent pure such as we used in the tuberculosis study, is no more painful than the best penicillin preparations

Dr Gold Is there any material on the market that is as pure as the standard against which the streptomycin of commerce is compared in the assay?

Dr McDermott No but I believe that the large manufac turers are soon going to have on the market material of about the same grade of purity as the highly purified material which we used

Dr Travell Will that increase the cost?

Dr McDermott It increases the cost to the manufacturers considerably because they lose about 50 per cent of the yield in the crystallization I doubt that it will materially increase the cost to the public in a competitive market if there is enough demand for it

Dr Pearlmutter Has streptomycin been given a trial in virus pneumonia?

Dr McDermott I do not know of any instances in which it has but I assume that it has I would certainly be opposed to using it in atypical pneumonia Although the drug is rela

tively non-toxic in comparison to some drugs, it is not innocuous and not to be used for self-limited, benign infections.

Dr. Gold: How does the problem of oral administration stand at the moment? Animal experiments show that it is absorbed by the oral route and that the fatal dose by mouth in mice is just about 3 times that by subcutaneous injection. I am wondering whether the situation here is analogous to the case of penicillin in which, if we give something like 5 to 10 times the parenteral dose, we may obtain perfectly satisfactory effects by the oral route. Have you any opinion about that?

Dr. McDermott: We have not pursued the subject because of the scarcity of the material.

Visitor: At Bellevue Hospital a series of typhoid carriers was examined. First, the drug was given intravenously. There was no conspicuous effect on the typhoid organism. There was a high incidence of renal toxicity among these patients. Then, some of them were given the drug orally. There was apparently less renal irritation. For a time the stool cultures were negative but subsequently reverted to positive. I am not certain of the range of dosage when it was given orally; I think it was of the order of twice the intravenous dose.

Another Visitor: Is it possible to inject streptomycin intramuscularly in wax and oil to avoid multiple injections as is now often done with penicillin?

Dr. McDermott: Unfortunately, that is not practicable because the amount of the drug which would be given in such a fashion would be too large, much greater than that in the case of penicillin.

Intern: At a recent therapy conference on urinary tract infections we were left with the impression that the sulfa drugs are far more useful in these infections than streptomycin. I wonder if you share those sentiments?

Dr. McDermott: In uncomplicated infection by Escherichia coli, which is the most common infection of the urinary tract seen by the internist and the obstetrician, I believe that sul-

absorption. Thus far, streptomycin has been found especially useful in urinary infections caused by the Escherichia coli and some other gram-negative bacterial infections of the urinary tract, such as the Bacillus lactis aerogenes, Bacillus proteus, and Bacillus pyocyaneus. It is highly effective in Friedländer's pneumonia, Hemophilus influenzae meningitis, and tularemia. It has also been found effective in pneumonias, abcesses, peritonitis, and other infections caused by the gram-negative bacteria frequently found in the urinary tract. It appears to be without value in virus infections. One of the most *stirring aspects of streptomycin action relates to tuberculosis:* the observation that it cures certain forms of animal tuberculosis, and the now well-established clinical experience showing that it may check some forms of human tuberculosis, especially those in the exudative stage. There was considerable discussion in the conference concerning the details of its rôle in the therapy of human tuberculosis.

Two other phases of streptomycin therapy received special consideration. There is some indication that different members of the same bacterial species show wide differences in susceptibility to streptomycin, and it is now well established that for most infections, resistance to streptomycin is acquired quite rapidly, in a matter of days to weeks. This limits the application of the drug to brief courses of treatment and necessitates the use of fully effective doses from the outset. The next point is the matter of toxicity. Streptomycin is not an innocuous drug. *In addition to the various allergic drug reactions* such as skin rash and fever, it may produce serious renal damage, it may affect the blood-forming organs, and it exerts an action on the central nervous system involving the vestibular apparatus and the eighth nerve, causing vertigo, tinnitus and impaired hearing. These effects, some of which are permanent, are apt to occur after prolonged use of the drug, after 3 or 4 weeks. They are more frequent with the larger doses, larger than those usually necessary. One needs to keep them in mind,

however, for the full scope of the applications of streptomycin has not yet been determined, and a good deal of exploration is still necessary to establish the full potentialities of streptomycin in human infections. In the present state of our knowledge, there is justification in giving streptomycin a trial in serious bacterial infections in which the other specific antimicrobial agents have failed. It is suggested that an *in vitro* test of the sensitivity of the organism may help to establish the indication for its trial in such cases.

Uses of Protein Hydrolysates

Dr Ephraim Shorr The protein hydrolysate is an outstanding addition to the list of therapeutic agents in recent years It has applications in several fields of medicine and surgery and for that reason we have here today experts in these fields to discuss the various aspects of the subject The problem of providing adequate energy for patients who are unable to take the requisite amount of foodstuffs by mouth has long been a matter of concern For many years parenteral alimentation was confined to the use of glucose and salts except for the occasional and purely experimental trials of other materials particularly fat This was the situation until a few years ago when as the result of the development of protein hydrolysates it became possible to provide essential amino acids by the parenteral route What was expected of the protein hydrolysates? Have these expectations been fulfilled? What are their uses and limitations? These are the points to be explored in the conference this afternoon The discussion will be opened by Dr Barr

Dr David P Barr As Dr Shorr has indicated one of the long sought goals in nutrition has been a diet which is completely adequate for maintenance and growth and which can be administered parenterally The need is apparent in the care of all those who cannot take food by mouth or who cannot absorb ingested foodstuffs Glucose salts and vitamins have so long been used by injection that the technics are commonplace, but it was not until 1938 that an adequate mixture of

amino acids was first successfully given by intravenous injection in humans The story of how this came about has considerable interest Many workers have contributed but I think we owe this development chiefly to the early investigations of Robert F Osborne and Lafayette B Mendel at Yale and to the very long and painstaking researches of William C Rose of the University of Illinois The observations of Osborne and Mendel were made years ago from about 1911 to 1914 Starting with the feeding of imperfect proteins gliadin and zein they discovered that two amino acids namely lysine and tryptophane were essential to normal growth Their discovery led to extensive investigations with similar methods and to the demonstration in 1928 by Rose and Cox that histidine was also essential Shortly thereafter Rose started research along another line namely that of feeding mixtures of the pure amino acids He found that although amino acids were added to the mixtures in the proportions in which they were thought to exist in the protein casein they failed to support growth as well as casein itself Rose s research led rather rapidly to a number of important discoveries (1) In addition to the previously recognized amino acids there was another which he called threonine and which was essential to growth (2) besides lysine tryptophane and histidine there were including threonine 7 other amino acids apparently indispensable for growth in rats a total of 10 essential amino acids (3) rats could grow and remain healthy without any of the other amino acids provided these ten were given (4) while the naturally occurring amino acids were effective in nutrition the synthetic optical isomers of some of them were ineffective

The following 10 amino acids were found to be essential in the rat lysine tryptophane histidine phenylalanine leucine isoleucine threonine methionine valine and arginine It was found that arginine could be formed to some extent in the body but not in sufficient amounts to support normal growth Amino acids other than these ten can apparently be

Uses of Protein Hydrolysates

Dr. Ephraim Shorr: The protein hydrolysate is an outstanding addition to the list of therapeutic agents in recent years. It has applications in several fields of medicine and surgery, and for that reason we have here today experts in these fields to discuss the various aspects of the subject. The problem of providing adequate energy for patients who are unable to take the requisite amount of foodstuffs by mouth has long been a matter of concern. For many years, parenteral alimentation was confined to the use of glucose and salts, except for the occasional and purely experimental trials of other materials, particularly fat. This was the situation until a few years ago when, as the result of the development of protein hydrolysates, it became possible to provide essential amino acids by the parenteral route. What was expected of the protein hydrolysates? Have these expectations been fulfilled? What are their uses and limitations? These are the points to be explored in the conference this afternoon. The discussion will be opened by Dr. Barr.

Dr. David P. Barr: As Dr. Shorr has indicated, one of the long-sought goals in nutrition has been a diet which is completely adequate for maintenance and growth and which can be administered parenterally. The need is apparent in the care of all those who cannot take food by mouth or who cannot absorb ingested foodstuffs. Glucose, salts, and vitamins have so long been used by injection that the technics are commonplace, but it was not until 1938 that an adequate mixture of

amino acids was first successfully given by intravenous injection in humans The story of how this came about has considerable interest Many workers have contributed, but I think we owe this development chiefly to the early investigations of Robert F Osborne and Lafayette B Mendel at Yale and to the very long and painstaking researches of William C Rose of the University of Illinois The observations of Osborne and Mendel were made years ago from about 1911 to 1914 Starting with the feeding of imperfect proteins, gliadin and zein, they discovered that two amino acids namely, lysine and tryptophane, were essential to normal growth Their discovery led to extensive investigations with similar methods and to the demonstration in 1928 by Rose and Cox that histidine was also essential Shortly thereafter, Rose started research along another line, namely, that of feeding mixtures of the pure amino acids He found that although amino acids were added to the mixtures in the proportions in which they were thought to exist in the protein casein they failed to support growth as well as casein itself Rose s research led rather rapidly to a number of important discoveries (1) In addition to the previously recognized amino acids there was another which he called threonine and which was essential to growth, (2) besides lysine, tryptophane, and histidine, there were, including threonine 7 other amino acids apparently indispensable for growth in rats, a total of 10 essential amino acids, (3) rats could grow and remain healthy without any of the other amino acids provided these ten were given, (4) while the naturally occurring amino acids were effective in nutrition, the synthetic optical isomers of some of them were ineffective

The following 10 amino acids were found to be essential in the rat lysine, tryptophane, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine and arginine It was found that arginine could be formed to some extent in the body but not in sufficient amounts to support normal growth Amino acids other than these ten can apparently be

synthesized in the body or dispensed with even in the growing animal.

One of the problems which complicated Rose's investigations was the fact that many of the essential amino acids are effective in nutrition only in their naturally occurring forms. For instance, he found that dextro-histidine could be converted in the body into the naturally occurring levo-histidine. On the other hand, this was not possible in the case of lysine. An immense amount of detailed investigative work was necessary to clarify the situation and to discover which amino acids had to be present in their natural form and which could be converted in the body. Rose presented an account of these researches in an important article in *Physiological Reviews* in 1938. He showed that in the case of the 5 amino acids, valine, leucine, isoleucine, lysine, and threonine, only the naturally occurring forms were utilized in nutrition, their isomers being ineffective.

Still other difficulties were encountered in the use of mixtures of amino acids in nutrition. A vast amount of work was necessary to determine exactly how much of each amino acid was required to maintain growth in humans. The cost of pure amino acids was so inordinately high that few could afford the luxury of maintaining nutrition by their use. The search for substitutes, for impure mixtures, was started at once and was pursued with great energy.

As you know, three methods have been employed for obtaining impure mixtures of amino acids: (1) alkaline hydrolysis, (2) acid hydrolysis, and (3) enzymatic hydrolysis. Each has presented practical difficulties. Alkaline hydrolysis is not practical because the exposure of protein to strong alkali leads to rapid racemization of the amino acids so that unnatural forms result. Acid hydrolysis leads to reactions in the mixture which destroy the essential amino acid, tryptophane. For this reason the few acid hydrolysates which are now coming on the market contain added tryptophane. The enzymatic hydrolysis

is slower and less complete and produces polypeptides in addition to amino acids There is always at least a theoretical danger of immunologically active split products of protein in an enzymatic hydrolysate

Other practical problems arise in the preparation and administration of mixtures of amino acids Melanin tends to form in some solutions If the pH is not correctly adjusted, the amino acids may cause acidosis The concentration of amino acids in solution must be so adjusted as to permit sufficient dosage without undue hydration of the body To establish nitrogen equilibrium dextrose must be included in appropriate amounts with the solution of amino acids

Chief consideration should perhaps be given to the enzymatic hydrolysate which is now in most common use Mead Johnson and Company was largely responsible for perfecting this material for parenteral administration As you may know, they hydrolyze the protein, casein, with pig pancreas, the enzymes of which convert both the casein and the proteins of the pancreas into amino acids and to some extent, into the lesser peptides The product, which they call amigen and which is now available in commerce, contains the essential amino acids in approximately the same percentages found in casein lysine 5 8, tryptophane 1 0, histidine 2 0, phenylalanine 5 6 leucine 13 5, isoleucine 4 8, threonine 4 5, methionine 3 0, valine 5 0 and arginine 5 5 It is important to know that amigen contains about 12 per cent of nitrogen and that about two thirds of this is in the form of amino acid nitrogen In other words 8 per cent of the amigen is amino acid nitrogen

To Robert Elman of St Louis a surgeon goes the credit for the demonstration that solutions of acid hydrolysates and of the enzymatic hydrolysate amigen can be given safely by intravenous injection in humans The amigen is supplied in the form of a powder from which solutions may be made, but it is, perhaps more satisfactory to use the solutions prepared by the

manufacturer; namely, the "amigen 5 per cent in 5 per cent dextrose solution," or the "amigen 10 per cent solution." These are so free of pyrogens and dangerous impurities that they may be given with almost as much safety as solutions of glucose.

A liter of a 10 per cent solution of amigen, containing 100 Gm. of the hydrolysate, supplies 366 calories from amino acids, *only a little less than the caloric value of a similar weight of* protein which would supply 410 calories. As in the case of protein, the hydrolysate has to be given with sufficient carbohydrate as an additional source of energy if nitrogen balance is to be attained. A solution containing equal amounts of amigen and glucose is unbalanced. Such a solution, namely, one containing 100 Gm. of amigen and 100 Gm. of glucose per liter, might be given to a patient with a very marked protein deficiency; but under such circumstances, it would probably be preferable to use plasma rather than the protein hydrolysate. For intravenous feeding over a considerable period of time, it is preferable to use each day 3,000 cc. of a solution containing 150 Gm. of amigen (544 calories) and 300 Gm. of glucose (1,230 calories), making a total of 1,774 calories per day. To this a requisite amount of salts and vitamins should be added. The following formula has been used by Albright and others: 3,000 cc. of fluid containing dextrose 300 Gm., amigen 150 Gm., sodium chloride 12.75 Gm., potassium chloride 2 Gm., vitamin C 50 mg., nicotinamide 75 mg., thiamine 5 mg., riboflavine 5 mg., pyridoxine 5 mg., vitamin K 2 mg., and calcium pantothenate 2 mg. With this as the only source of food, they were able to maintain caloric and nitrogen equilibrium over considerable periods, the quantities appearing to represent a complete feeding for a 24-hour period for a person of average size. The solution is given by a continuous intravenous drip using a standard infusion apparatus. There are several difficulties which include the undesirable limitation in the activity of the patient, the need for constant attention of the doctor,

and the danger of venous thrombosis from prolonged injection Intravenous alimentation of this kind must be given at a slow rate, and 1,000 cc of such a mixture should not be introduced in less than 2 hours When properly administered, disagreeable reactions are surprisingly few There may be some loss of appetite, sometimes nausea or vomiting and occasionally flushing When oral feeding is also used, the intravenous injections should be given after meals to avoid interference with appetite Although intravenous alimentation is always undesirable, its achievement in practical form represents a therapeutic triumph

Dr Shorr Dr Glenn of the Department of Surgery will now discuss the protein hydrolysates from the standpoint of the surgical problems

Dr Frank Glenn We may briefly classify surgical patients, from the standpoint of the need for proteins, into three groups, namely, those who are deficient in proteins prior to operation, those who develop the hypoproteinemia during the operation, and, finally, those in whom the problem arises in the postoperative period The first group includes patients who are unable to take food or suffer with a disturbance of the digestive apparatus giving rise to impaired absorption or losses due to other causes In this group are to be found patients with gastrointestinal ulceration tumors regional ileitis and colitis In patients with severe infection, there may be reduced intake of proteins or increased destruction Patients with hyperthyroidism may develop a protein deficiency as the result of the increased metabolism even though their protein intake be high Patients with acute surgical conditions due to injury may develop a deficiency because of blood loss and shock Protein loss may be very high in patients with burns Before any surgical procedure is embarked upon in a patient with hypoproteinemia it is of great importance to restore the protein level The operative procedure itself may give rise to hypoproteinemia partly as the result of hemorrhage and partly as the re-

sult of the anesthesia The anoxia associated with anesthesia may lead to loss of plasma through increase in the permeability of the capillaries Also, impaired metabolism of the liver cells may take place and in this way give rise to impairment in the synthesis of serum proteins After the operation, patients lose nitrogen in excess of that lost by the normal individual This is partly due to the reduced intake of food, but the loss is greater than can be accounted for by this factor alone Fever, vomiting, hemorrhage, and surgical drainage all contribute to a loss of protein, but there is a decrease in nitrogen retention in patients even without these avenues of loss The decrease may be very considerable and may amount to from 1 to 5 pounds of body weight when they are kept in bed for a period of 7 or 8 days The problem represents a wasting of muscle due to inactivity

The loss of protein in the postoperative period is unfavorable to recovery The hypoproteinemia affects the postoperative course in several ways It may give rise to pulmonary edema with the increased tendency to pulmonary infection and pneumonia It may interfere with the healing of wounds in degrees varying from slight impairment of the maturation of fibroblasts to the more extreme cases showing no tissue reaction and dehiscence of the wound Lowered resistance to infection probably occurs indirectly through impaired detoxifying action of the liver and impaired production of the globulin fractions of proteins which are related to the immune bodies It also promotes edema of the gastrointestinal tract following surgical procedures and that in turn interferes with the functioning of stomas and restoration of the continuity in the case of gastric resections This edema may be sufficient to prevent food from passing through stomas which are mechanically large enough Likewise, it tends to interfere with the peristaltic action of the gastrointestinal tract

We should pay special attention to the difficulty of determining the true content of serum proteins in the surgical pa

tient The protein concentration of the serum is often deceptive in the case of the patient who has been dehydrated by vomiting or diarrhea

A favorable nitrogen balance is of the first importance in surgical patients Hypoproteinemia should not be permitted to exist or develop In the preoperative period much may be accomplished by blood transfusions plasma intravenous amino acid mixtures such as amigen and protein hydrolysates given orally In the anemic patient it is probably wise to discontinue the use of blood transfusions as soon as the red cell count has been restored to normal The use of plasma for maintaining a favorable protein balance is expensive The cost of the protein hydrolysates is more moderate Many patients can take these by mouth if they are properly prepared If the oral route is not feasible they may be given by intravenous injection as described by Dr Barr During operation blood transfusions and plasma are probably most effective for maintaining ample protein reserve In the postoperative period many patients require protein by intravenous injection during the first 18 to 72 hours in order to maintain a nitrogen balance This may be accomplished by the intravenous use of blood plasma or amigen Subsequently the protein hydrolysate may be given by mouth and after the use of the predigested foods for a short period regular foods which may be classified as simple from the standpoint of digestion may be resumed

In the past there has been a tendency to overinvalidize surgical patients and the long period of inactivity resulted in depletion of protein stores The pendulum is swinging in the opposite direction but although it is wise to reduce the period of inactivity to a minimum we should not overlook the fact that these are not normal people The inordinate loss of proteins in the postoperative period is controlled by the present trend to mobilize patients earlier and to make use of the predigested foods shortly after operation

Dr. Shorr: Dr. Glynn, what uses do you make of protein hydrolysates in pediatric practice?

Dr. Martin J. Glynn: We encounter the same general indications for the use of protein hydrolysates as have been described for adult medical cases by Dr. Barr and for surgical cases by Dr. Glenn. I should like to remark briefly about four conditions, perhaps more common in pediatric practice.

The youngster with severe diarrhea presents the most serious problem which calls for the use of these agents. These cases are treated by prolonged starvation, which in a young infant is a period of the order of 2 to 4 days. These youngsters appear to tolerate prolonged starvation quite well, but it is my impression, and that of other workers, that the use of protein hydrolysates is decidedly helpful. In the treatment of this condition, the first step is to restore the electrolyte pattern, the water balance, and the plasma proteins to normal by the use of whole blood and plasma. After this is done and the circulation is in good condition, the protein hydrolysate may be given safely by hypodermoclysis. Specifically, the patient receives 40 cc. per Kg. of amigen 5 per cent in 5 per cent dextrose solution twice a day by hypodermoclysis, in addition to 35 cc. per Kg. of 5 per cent dextrose solution by intravenous infusion twice a day. The treatment provides a total of 45 calories per Kg., 15 in the form of amino acid and 30 in the form of dextrose. This is by no means maintenance, but it is a helpful step in that direction. I do not know of any studies on the fate of the amino acids which are provided by this regimen.

In eczema, we utilize amino acid therapy for a different purpose, namely, in an attempt to supply a source of protein with a minimum potential for allergic reactions. In severe eczemas, about 50 per cent may be expected to show considerable improvement, and in some, the control of the eczema is complete. The treatment is also worth trying in the mild eczemas of older infants. It is the impression of one observer, who tried it in mild eczemas of very young infants, that fewer of these de-

veloped severe eczema. The protein hydrolysate may be given parenterally, but in eczema we are more likely to use it orally. We have used a mixture containing amino acids 20 per cent, carbohydrate up to 50 per cent, and fat 18 per cent, diluted so as to make an appropriate formula. Articles least likely to produce allergic reactions were used; for example, olive oil in the case of the fat, and in the case of the carbohydrate, arrowroot starch and dextrimaltose. Formulas based upon these materials can be made up in much the same way as the usual formula with milk so as to meet the requirements.

We occasionally use protein hydrolysates to advantage in the nephrotic syndrome. These patients often develop the so-called nephrotic crises, episodes of severe infection in the form of peritonitis, septicemia, or both. We used them a great deal before the effective antibiotics were available; the intravenous amino acids seemed to influence the course favorably. A youngster who does not respond as expected to penicillin or sulfadiazine should be supported with protein hydrolysates.

There is a miscellaneous group of conditions in which amigen is often used by mouth with results that can be described as no more than encouraging. They include cases of young babies with persistent vomiting from obscure cause. A mixture containing amigen 3.5 to 5 per cent and 5 per cent carbohydrate may be given in such small amounts as are fairly well tolerated. It may be gradually replaced by the more sustaining types of nourishment. This mixture is also advocated for the first oral feedings after therapeutic starvation in cases of diarrhea.

The other conditions, occasionally encountered in the pediatric group, are more frequently seen in adults. These are postoperative troubles, trauma, and burns. Their treatment is the same as in adults.

Dr. Barr: It would be interesting to hear from Dr. Glenn about the use of amino acid mixtures in the treatment of burns. After a burn of moderate degree, a person may lose as

much as 40 Gm of nitrogen in 24 hours The loss may continue during the ensuing days because of increased capillary permeability

Dr Shorr The subject is now open for general discussion I saw your hand raised, Dr Gold

Dr Harry Gold Could we have some discussion on the utilization of amino acids? There is abundant proof that their use can establish a positive nitrogen balance This indicates that nitrogen is being retained by the body But what is the body doing with the nitrogen? Is it converting it into the proteins which are most needed? There is an infinite number of proteins those of the skeletal muscles liver blood heart muscle, and many others The loss of proteins in disease may be due to defective supply, but it may also be due to defects in the bodily mechanisms for the synthesis of specific proteins a defect which might not be corrected by any amount of extra supply How does the evidence stand on some of these points? Suppose we first consider the question of regeneration of blood proteins in a case of hypoproteinemia

Dr Shorr I have the same questions What actually happens to hydrolysates given intravenously to a patient with severe trauma burn shock operative procedures or infection? Is there any evidence that the body utilizes the nitrogen? In what condition is it not utilized? Are we justified in assuming that what goes into the vein is actually available for the nutritional requirements of the patient particularly the very ill patient whose needs are greatest?

Dr Samuel Z Levine It is my understanding that Dr Whipple has shown that the amino acids are as satisfactory as plasma in raising the plasma protein levels in dogs which have been exsanguinated by his technic Am I correct in that, Dr Barr?

Dr Barr When the level of blood protein has been artificially reduced by plasmapheresis or by inadequate diet amino acid mixtures and plasma are exceedingly effective in

raising the level of serum proteins If, on the other hand, the low level of blood proteins is due to defective formation, as in disease of the liver, the administration of plasma or of amino acid mixtures does not correct the deficiency Neither agent is more than moderately effective in the hypoproteinemia of nephrosis

Dr Gold That seems to me to be a very important point to remember We encounter many cases of hypoproteinemia, as in advanced heart failure, cirrhosis of the liver, and other conditions, in which an intensive course of treatment with amino acids has been given It accomplishes nothing because, in these conditions the liver seems to possess no power to synthesize the protein

Dr Glenn In general, we have been unable to elevate serum proteins in patients by the intravenous administration of amino acids I have the strong belief that we can prevent patients from failing by the use of amino acids when they are unable to take food In a patient with a lowered serum protein value, the most effective way of elevating it is by means of blood transfusions and plasma

Visitor Since there are these limitations in the effectiveness of protein hydrolysates, should we rely on such methods of alimentation, or is the use of whole blood or plasma always preferable?

Dr Barr Experience indicates that with normal animals and with normal individuals it is possible to maintain nitrogen equilibrium and normal weight solely by means of protein hydrolysates This does not mean that the same results will be obtained in a very sick person or in a person who has been damaged by shocking experiences Nothing that we can do by such alimentation will maintain nitrogen equilibrium in a patient with a recent colectomy or other comparably severe operation on the gastrointestinal tract There have been some observations made on patients immediately after appendectomies which indicated that fairly small infusions of hy-

drolysates were able to maintain nitrogen equilibrium over 6 day periods On the other hand, in the same series patients with colectomies, gastric resections, or other serious operations, similarly treated, lost nitrogen in amounts up to 140 Gm during the same period These observations indicate that the response which is seen in normal individuals can be duplicated in patients only if the damage or shock has not been too great

Dr Shorr I think you have hit the point about cases that fail to respond The nature and the degree of stress on the organism determine the response to intravenous alimentation Studies were carried out in severe infection and after trauma and it was found that all the nitrogen administered as amino acids appeared in the urine in 24 hours This went on for days One has the illusion that protein has been supplied but there is clear evidence that it is being deaminated and does not remain as protein in the organism

Dr Barr Are there any comparable observations on the fate of protein itself?

Dr Shorr Yes there are for infusions of plasma Here the protein remains in the body longer and is degraded by a slower mechanism

Dr Barr Is it not excreted as urea?

Dr Shorr It is eventually, but it is released apparently slowly enough to be more available for the maintenance of nitrogen equilibrium

Dr Walter Modell Is there any difference in the time needed to elevate the plasma protein level by means of amino acids and the time it takes by plasma infusions assuming of course a case in which either one or the other could be used?

Dr Barr I do not think there is very much difference

Dr Shorr Might it not depend Dr Barr, on the state of the subject? In the normal animal in which the plasmapheresis experiments were conducted all the normal capacities to synthesize proteins from amino acids were retained in patients

suffering with a variety of infections or wounds however varying degrees of defects in the capacity for protein synthesis might obtain Under such conditions the organism might hold on to injected plasma proteins so that the blood level could be satisfactorily raised whereas injected amino acids might be much less efficiently utilized

In relation to your point Dr Gold that the retention of nitrogen after the administration of amino acids is an established fact it is well to remember that in many cases neither oral nor parenteral administration of the usual amounts of protein in the diet gives rise to a positive balance It is only after extraordinary amounts such as Co Tui for example used in his patients after gastrectomy 350 to 450 Gm of protein per day that a positive balance appeared As I have already indicated in the patient with disease receiving a parenteral infusion of amigen calculated to maintain a protein balance every bit of the nitrogen often is excreted in the urine within the same day in the form of ammonia or urea There is a problem here which remains unsettled Of course it has nothing to do with the usefulness of this procedure as a supplement to oral feeding But it does bring up the question of the nature of the disturbance in disease which is responsible for such rapid breakdown and wastage of nitrogenous materials

Dr Barr I should like to hear from Dr Shorr some comment on the reason for the tremendous loss of protein which occurs following injuries such as fractures burns acute infectious diseases or almost any other insult to the body There are records of patients who during a 10-day period after operation have lost as much as 100 to 180 Gm of nitrogen corresponding to 2 5 to 4 5 Kg of muscle A surprisingly great loss occurs often in uncomplicated anesthesia Why should the body lose nitrogen under such circumstances?

Dr Shorr It would be very nice if there were an answer There are a number of possible explanations One clinical observation may be cited namely that patients may or may not

lose protein excessively under these circumstances and that, whether they do so or not, depends on their nutritional state, a highly undernourished individual may undergo an experience of this sort without loss of protein Cuthbertson showed this very clearly in his experimental animals Why does the debilitated individual not lose protein when the well nourished person may have a negative nitrogen balance of 30 Gm on a daily ration of 150 Gm? The explanation possibly involves the concept that there is *one type of protein which is a* little more specifically a part of the chemical structure of the cell, and another type which is, shall we say, in the nature of a *reserve or depot protein in the old fashioned sense* It would look as if the debilitated individual were down to his basic protein stores and for that reason would not readily lose more, while the well nourished individual would readily lose protein to the extent of his extra protein reserves In addition, hormonal factors may play a rôle This process which takes place in the course of the first 3 weeks after an insult, such as infection or a fracture with recovery, may involve the action of hormones which have to do with protein metabolism and the reparative process, namely, the glycotropic and androgenic adrenal cortical hormones It has been shown by Selye that, after any kind of stress or damage, an extraordinary change in the adrenal cortex takes place, it looks as if one had completely released its lipoids and with them its cortical hormonal content Under the influence of stress it is known that certain of these hormones are capable of breaking down protein excessively and forming carbohydrate from the non nitrogenous residues Support for this concept, as applied to the human, has been supplied by Browne and his associates Venning and Browne have found these cortical hormones in the urine in great excess after infections such as pneumonia after operations, after fractures and, in fact, after all manner of stress and exposure

Testosterone and its end products, the 17 ketosteroids,

which we also measure in urine, have been demonstrated by Kenyon and others to promote the storage of proteins Individuals who receive these androgens store protein unusually well, both normal individuals and those, such as hypogonadal males, who have a lack of androgenic hormones It has been found that the level of 17 ketosteroids is characteristically low during the phases of an illness or damage when the level of adrenal cortical hormones is high It looks as if these two factors, a depression in the elaboration of protein storing hormones and an increase in the elaboration of protein degrading hormones, may play a part in the unusual loss of protein during recovery

Dr Barr Much emphasis is now given to the loss of serum proteins which takes place during short periods Surgeons particularly, have regarded such loss as justification for protein administration Their reasons Dr Glenn has brought out very clearly One wonders however, whether the consequences which are feared actually occur, whether it is so dreadful for the protein of the circulating blood to fall by 10 per cent, which will happen after 48 hours of starvation and whether such a mishap must be corrected at once by the administration of plasma, albumin or amino acids I doubt that the actual necessity has been demonstrated but I should like to hear Dr Glenn's opinion

Dr Glenn I think that the loss of a certain amount of protein in the normal individual as Dr Barr says, is probably not of great importance, but in an individual who is already depleted the further lowering may cause trouble and may account for the difference between a wound that will heal and one that will not I believe that the intravenous administration of proteins exercises a kind of sparing action

Dr Shorr I am inclined to agree that there is very little proof that a small reduction in blood proteins in surgical cases is of importance, and that we may be going too far in our measures to correct this condition It would seem reasonable,

lose protein excessively under these circumstances and that, whether they do so or not, depends on their nutritional state, a highly undernourished individual may undergo an experience of this sort without loss of protein Cuthbertson showed this very clearly in his experimental animals Why does the debilitated individual not lose protein when the well nourished person may have a negative nitrogen balance of 30 Gm on a daily ration of 150 Gm? The explanation possibly involves the concept that there is one type of protein which is a little more specifically a part of the chemical structure of the cell, and another type which is, shall we say, in the nature of a reserve or depot protein in the old fashioned sense It would look as if the debilitated individual were down to his basic protein stores and for that reason would not readily lose more, while the well nourished individual would readily lose protein to the extent of his extra protein reserves In addition, hormonal factors may play a rôle This process which takes place in the course of the first 3 weeks after an insult, such as infection or a fracture with recovery, may involve the action of hormones which have to do with protein metabolism and the reparative process, namely, the glycotropic and androgenic adrenal cortical hormones It has been shown by Selye that, after any kind of stress or damage, an extraordinary change in the adrenal cortex takes place, it looks as if one had completely released its lipoids and with them its cortical hormonal content Under the influence of stress, it is known that certain of these hormones are capable of breaking down protein excessively and forming carbohydrate from the non nitrogenous residues Support for this concept, as applied to the human has been supplied by Browne and his associates Venning and Browne have found these cortical hormones in the urine in great excess after infections such as pneumonia, after operations, after fractures and, in fact, after all manner of stress and exposure

Testosterone and its end products, the 17 ketosteroids,

which we also measure in urine have been demonstrated by Kenyon and others to promote the storage of proteins Individuals who receive these androgens store protein unusually well both normal individuals and those such as hypogonadal males who have a lack of androgenic hormones It has been found that the level of 17 ketosteroids is characteristically low during the phases of an illness or damage when the level of adrenal cortical hormones is high It looks as if these two factors a depression in the elaboration of protein storing hormones and an increase in the elaboration of protein degrading hormones may play a part in the unusual loss of protein during recovery

Dr Barr Much emphasis is now given to the loss of serum proteins which takes place during short periods Surgeons particularly have regarded such loss as justification for protein administration Their reasons Dr Glenn has brought out very clearly One wonders however whether the consequences which are feared actually occur whether it is so dreadful for the protein of the circulating blood to fall by 10 per cent which will happen after 48 hours of starvation and whether such a mishap must be corrected at once by the administration of plasma albumin or amino acids I doubt that the actual necessity has been demonstrated but I should like to hear Dr Glenn s opinion

Dr Glenn I think that the loss of a certain amount of protein in the normal individual as Dr Barr says is probably not of great importance but in an individual who is already depleted the further lowering may cause trouble and may account for the difference between a wound that will heal and one that will not I believe that the intravenous administration of proteins exercises a kind of sparing action

Dr Shorr I am inclined to agree that there is very little proof that a small reduction in blood proteins in surgical cases is of importance and that we may be going too far in our measures to correct this condition It would seem reasonable

however, to attempt to restore blood proteins in cases in which they have fallen considerably. But there is another question which needs consideration, namely, how far we should go in attempting to establish a positive nitrogen balance in patients whose plasma protein levels are normal. Consider, for example, the patients with peptic ulcer who are now treated with amino acids. Vast quantities are necessary to establish a positive nitrogen balance in some of these. Is the positive nitrogen balance established in such cases beneficial to the course of the disease? I do not believe that we have the answer to this question. It certainly can be said that patients with fracture recover and do extremely well at a time when they have regained only a small fraction of the protein lost during the illness.

Dr. McKeen Cattell: The use of amigen has been extensively discussed. I want to ask whether other protein hydrolysates which are available are not equally satisfactory, or whether there is some preference for this particular brand.

Dr. Barr: It is quite probable that the mixture which is called amigen may be duplicated or improved. Many similar preparations have been offered and are now undergoing clinical trial. Since there are many pitfalls in the preparation of amino acid mixtures, actual clinical experience is needed with each new product, and it is becoming increasingly difficult to find investigators who are interested in testing a new mixture to determine whether it is as good as one which is known to be satisfactory. Many tests are necessary: Ability to support normal growth must be demonstrated; absence of immunologically active fractions must be established; since mixtures of amino acids furnish an excellent culture medium, bacterial contamination must be excluded; finally, the solutions must be free of pyrogens and other impurities. I mention these requirements to indicate how difficult it is to be sure that a new preparation of a protein hydrolysate is as satisfactory as one which has already been tested.

I think that Dr. Almy has had some experience with an acid hydrolysate

Dr Thomas P. Almy We used the preparation of Stearns and Company, parenamine 6 per cent, in two patients It was well tolerated when injected at a rate similar to the rate at which we administer amigen It is more acid than the parenteral amigen preparation the pH is 5 5.

Dr Shorr Perhaps Mr Clarke, our pharmacist, would say something about the various preparations now available

Mr Donald A Clarke The following list of preparations is presented with the stipulation that it will probably be out-of-date in the near future, for not only are new preparations being added but the old ones are being altered

I know of only two acid hydrolysates parenamine (Stearns) made from casein, and aminosal (Abbott) made from beef blood fibrin, both intended for parenteral use No alkaline hydrolysate is available All the others are enzymatic hydrolysates Amigen (Mead Johnson) which is made from casein has already been mentioned It is presently available only for parenteral use although the original preparation was also used orally Their oral preparation is called protolysate and is made from casein Here is a partial list of other oral preparations aminoids (Arlington) from milk, beef, wheat, and yeast, aminoprote (U S Vitamin) from beef, casein, lactalbumin, and yeast, lactamin (Wyeth) from lactalbumin, ledinac (Lederle) from liver, protein hydrolysate MRT (Thompson) from yeast, protein hydrolysate (Squibb) from casein Some of these preparations are already mixed with some form of carbohydrate There are many other preparations not listed, which contain, in addition to hydrolyzed protein of some kind and carbohydrate, some other substances such as minerals, vitamins flavoring materials and, in one case, olive oil

The parenteral preparations are usually provided as sterile solutions with added dextrose Several concentrations of each are generally available, usually in the range from 5 to 10 per

cent. The oral preparations are most commonly available in the form of a powder, and sometimes in the form of granules. Flavored solutions are obtainable, and one manufacturer supplies an enteric-coated tablet.

Dr. Gold: It might be worth while calling attention to the fact that there are protein hydrolysates on the market substantially free of sodium chloride. This is of some importance in the problem of feeding a patient with congestive failure. I know of one such preparation, protein hydrolysate-MRT. It is not to be confused with the other preparation by the same manufacturer which contains 6 per cent sodium chloride. There is another preparation called protinal (National Drug) which is said to be very low in sodium chloride. There are other similar preparations.

In connection with the choice of preparations, it might be worth mentioning the experimental observation that the composition of a mixture of amino acids has a bearing on the extent to which it is utilized in the body to form proteins. It has been shown that if one omits an essential amino acid, an otherwise adequate mixture will fail to be utilized, and that the defect in utilization cannot be corrected if several hours elapse before the missing amino acid is supplied. This is a challenge to the preparations of protein hydrolysates; a proper mixture must be made available to the tissues at one time if the mixture is to prove effective. This is perhaps one of the reasons why, as Dr. Barr has pointed out, it is necessary to test a new hydrolysate for its capacity to support growth. This may also have bearing on the question of the utility of protein hydrolysates in patients with evidence of protein deficiency who may be able to consume large quantities of proteins in the form of ordinary foods. We do not have satisfactory clinical evidence concerning this point; but the possibility must be considered that such patients may suffer with difficulty in protein digestion, so that an adequate mixture of amino acids does not become available in the blood stream, adequate in the sense of

relative proportions of different amino acids being present at the proper time to enable the tissues to utilize them for the synthesis of tissue proteins

Dr Charles H Wheeler From talking with the house officers some time ago, Dr Barr, I gained the impression that they were still dissatisfied with the solutions of amigen There were frequent pyrogenic reactions Am I misinformed about that?

Dr Barr When Elman started to use amigen, he encountered some quite alarming reactions consisting of fever, nausea and vomiting As preparations improved and the rate of injection was slowed, he finally attained a record of the injection of many liters without any reactions The absence of pyrogens in the solution and slow injection are factors of the greatest importance in the avoidance of reactions

Dr Levine The experience at Washington University has been very satisfactory Intravenous and subcutaneous injections have been given to a large number of infants and young children without significant reactions Our early experiences in smaller numbers were not so favorable The children developed fever and some went into collapse The house staff became reluctant to use it Matters have improved, however, with the more recent preparations and slower injections

Dr Gold It seems from the literature that the number of serious accidents following parenteral amino acid injections is not very large There was a report by Curreri and associates in the *J A M A* , July 7, 1945 in which they encountered one fatality after about 2,000 administrations The patient received the intravenous infusion of the usual preparation for 2 days without trouble, but on the third day developed a shock like reaction with hyperthermia and died 40 hours later They stressed the desirability of making someone in the hospital responsible for supervision of these infusions in order to insure that the solution is clear, that the rate of injection is slow, that the amino acid solutions are not mixed with materials of high pH such as sodium salts of the sulfa drugs which give rise to

precipitation, and that the unused contents of the bottle which has been opened are discarded There seems to be the possibility that bacterial contamination in open bottles may give rise to toxic amines Bacterial contamination is one of the points which Dr Barr has stressed

Visitor Has there been any sloughing in the case of the hypodermoclysis?

Dr Glynn We encountered one case of extensive sloughing in approximately 1,000 such treatments

Dr Gold In regard to the toxicity of amino acids you may be interested in some observations which were made by Riker and myself a few years ago in a study of sodium hydroxyacetate in which we also tested the amino acid, glycine One is inclined to regard the amino acids as harmless since they are essential products of normal metabolism, but we discovered that glycine may act as a poison in cats and dogs as little as 1 Gm per Kg injected intravenously in cats gave rise to drooling muscular weakness hyperexcitability, and dilatation of the pupils with failure to respond to light, an oral dose of 6 Gm per Kg in a dog caused similar symptoms with convulsions and death in 4 hours Clearly the amino acids are not harmless substances

Dr Shorr What has been your experience with reactions Dr Almy, in the management of ulcerative colitis in which the intravenous route was used?

Dr Almy Our experience in one patient has been grim Alimentation exclusively by intravenous route for a week resulted in thrombosis of all accessible veins I was told by Dr Albright that if one escapes this difficulty, one may begin to see remission of the acute symptoms after one week of this treatment

Dr Barr It might be interesting to hear of Dr Almy s experience with the oral use of the amino acids in ulcerative colitis The discussion thus far has dealt chiefly with intravenous alimentation which, perhaps, has less application than the oral route

Dr Almy In ulcerative colitis, the intravenous administration of hydrolysates has always appeared more attractive because it avoids the use of the colon as a conduit of food residue; however, we have tried large amounts of the hydrolysate orally in these protein starved patients We gave them 5 to 6 Gm of amigen per kg per day by mouth, together with dextrimaltose, in a manner comparable to that used by Co Tui in the treatment of peptic ulcer The results were not as striking as I had hoped they would be In a small group of a dozen patients, 30 per cent showed a rapid gain in weight to the extent of about 3 to 5 Kg, and progressive improvement resulted The other cases remained uninfluenced This form of alimentation caused severe diarrhea in these patients, and it is noteworthy that in spite of it the gain in weight took place

Visitor How successful is the retention enema of amigen?

Dr Freddy Homburger We have been using retention enemas of a Squibb casein hydrolysate which is roughly comparable to amigen and, when given with proper technic and care it has achieved positive nitrogen balance over a fairly long period of time It was not found possible to achieve this in all patients but in about one third of the patients it was successful

Dr Shorr And what is the proper technic?

Dr Homburger The rectum should first be cleansed very carefully with a small water enema Only small quantities at a time should be used Instead of the ordinary rectal tube, a urethral catheter should be inserted to about 10 or 12 inches. We use a Murphy drip for about 1 to 2 hours to give 400 cc. of the solution which contains about 100 to 150 Gm of hydrolysate in 5 per cent dextrose Usually the first day there is some irritation, but when the patient is accustomed to the procedure, the enema may be retained, and nitrogen balance may be maintained

Dr Shorr Where do you think the resorption takes place? In what part of the large gut?

Dr. Homburger: I think that the resorption takes place in the lower portion of the large intestine where water is known to be resorbed.

Dr. Shorr: Not in the rectum?

Dr. Homburger: In the sigmoid, I think. We have evidence only for the fact that the nitrogen contained in the administered material is retained.

Dr. Gold: The protein hydrolysates may therefore be given by various routes, oral, subcutaneous, rectal, and intravenous. There are reports of its satisfactory use by the intrasternal route directly into the bone marrow by means of the Turkel needle. The needle may apparently be left in place for 24 hours or longer and the material may be administered as rapidly by this route as by the intravenous route, about 1 to 2 Gm. of amino acid nitrogen per hour.

Dr. Shorr: This is an extensive subject and there are many more points which need to be considered, but our time is up. Perhaps the interesting topic of protein hydrolysates in peptic ulcer may be taken up at another conference.

SUMMARY

Dr. Gold: We may now bring together a few of the salient points which were elaborated in the conference this afternoon. [illegible] com- [illegible] as infections, operations, anesthesias, malignancy, burns, hyperthyroid states, diarrheas, and prolonged inactivity. It is clearly manifest when there is extensive body wasting, but it is earlier detected by an increased loss of nitrogen of varying degrees, which often reaches alarming proportions. The circumstances are frequently such that an adequate supply of proteins in the form of the usual foods, and the use of the regular channels for their consumption, are not feasible. Great interest has, therefore, been aroused in the discovery about ten years ago that it is possible to prepare appropriate mixtures

of amino acids in the form of protein hydrolysates, suitable for all the common routes of administration, and to use them as a source of bodily proteins This appears to be a development of major importance, the culmination of experiments covering a period of nearly forty years It supplies the missing link, the protein the others being carbohydrates, fats, and vitamins, in the long quest for complete intravenous alimentation

There was not sufficient time to consider all the conditions in which the protein hydrolysates may be applied, but the discussion indicates that they have already been put to use extensively in a wide variety of conditions associated with an unfavorable protein balance In the conference, the surgeon discussed their uses preoperatively and postoperatively in relation to extensive surgical procedures, traumas, hemorrhage, and anesthesia The pediatricians discussed their value in the treatment of diarrheas of infants, in the nephrotic syndrome, and in eczema as a source of protein with minimum potential for allergic reactions They seem to be of great value in patients with burns who lose alarming quantities of protein, of some value in edema associated with hypoproteinemia, in ulcerative colitis peptic ulcer, and in nutritional problems in which only parenteral alimentation is feasible This is but a small part of the list of conditions in which the protein hydrolysates have been recommended and used as a means of promoting recovery from states of ill health

Enthusiasm for the use of protein hydrolysates has naturally run very high and as experience has increased and the problem has received more intensive consideration, numerous questions have arisen How strong is the evidence for the utility of the protein hydrolysates in a large proportion of the conditions in which they are now used? Are we assigning too many troubles to the moderate reductions in blood protein levels and negative nitrogen balance which occur so commonly? Is the zeal for establishing nitrogen equilibrium or positive nitrogen balance in many of the conditions in which

they are now recommended justified by the results? Since such restorations seem theoretically correct, there is the danger of carrying the application of protein hydrolysates far beyond the point of satisfactory evidence that they are actually useful

On the theoretical side, questions have been raised as to what the body does with the amino acids administered in the form of protein hydrolysates In normal individuals the evidence is strong that, when they are administered sufficiently slowly and in proper composition, they are stored and converted into proteins, but much remains to be learned about abnormal states in which the basic difficulties may lie in defective mechanisms for converting amino acids into the infinite number of proteins Then, there is the question whether the administration of hydrolysates serves merely to spare body proteins or whether it exerts some other type of beneficial actions Why does the body lose protein so rapidly in such conditions as protracted bed rest anesthesia, and operative procedures in which there may be apparently little blood loss or tissue destruction? An interesting viewpoint was presented that an endocrine imbalance involving the cortical hormones of the adrenal and the androgens may be responsible for the marked loss of proteins in certain states of bodily stress

The answers to some of these questions have not been entirely satisfactory, but the exploration of these and others in the discussion this afternoon has helped to reveal the complexity of the problem, and to provide some insight into the reasons for the numerous failures to accomplish expected results In disease states the simple loading of the system with amino acids falls far short of correcting many of the conditions It was pointed out, for example, that hypoproteinemia in surgical problems is much more often corrected by plasma or blood infusions than by intravenous hydrolysates and that in the prolonged starvation in infant diarrhea, it is imperative first to restore the blood protein level by plasma infusions before attempting to maintain the gains by parenteral protein

hydrolysates Much careful observation will be necessary in order properly to sift out the practical from the large volume of theoretical indications

The parenteral administration of protein hydrolysates is not without risks The improvement in the preparations of commerce and the slowing of the rate of administration have greatly reduced serious accidents although minor unpleasant reactions are fairly common Suggestions have been made for avoiding disasters in the routine use of intravenous protein hydrolysates in hospital practice

The choice of preparations is of considerable importance especially in relation to those for intravenous injection Many of the preparations now on the market show great improvement in composition freedom from pyrogens and allergenic peptides but the matter of preparations is in a state of constant flux the ideal preparation is not yet available

The discussion also included such topics as a formula for complete intravenous alimentation dosage for oral use and the various routes of administration

Management of Peptic Ulcer with Protein Hydrolysates

Dr Thomas P Almy About two years ago, we had the pleasure of listening to a symposium on peptic ulcer We heard from a medical man who recommended surgery in the management of ulcer We heard from a surgeon who recommended conservative medical management We also heard from a person high in the councils of surgical research, who recommended a nutrition program for the treatment of ulcer We carried away from this symposium not only a wealth of understanding of the problem of ulcer which we did not have before, but also a feeling that the approaches to the therapeutic problem were being broadened The principal speaker this afternoon has a new concept in the management of peptic ulcer Dr Frank Co Tui, of New York University College of Medicine, will describe his method of treatment of ulcer by hyperalimentation and the use of protein hydrolysates

Dr Frank Co Tui It was in the course of preparing patients with peptic ulcer for operation, usually gastric resection that we gave them protein hydrolysates in order to build them up In 4 patients, the pain subsided and a gain in weight took place The results were so striking that we thought we accidentally had unearthed an important discovery We then tried it in 30 hospitalized patients who were intractable to the Sippy treatment or to amphojel with or without antispasmodics The patients were not on complete bed rest but were allowed to be up and about We put them on the system of hy

peralimentation This consisted of 0 6 Gm of nitrogen per Kg. in the form of protein hydrolysate in addition to enough carbohydrate to make a total of 50 calories per Kg In accordance with this formula, a 70 Kg man received 3,500 calories a day. Since the hydrolysate which we used contained 12 per cent nitrogen, such a patient received approximately 350 Gm of hydrolysate, representing about 1,400 calories The balance of the calories was made up by about 500 Gm of a sugar, such as dextrimaltose In this series of cases pain either subsided or markedly diminished within 48 hours There was prompt gain in weight of as much as a pound a day, and there was a feeling of well being We also thought there was X ray evidence of early healing Upon discharge, one half of the patients continued dietary precautions and the others did not We soon learned that the treatment did not prevent recurrences for of those that took no subsequent dietary precautions, 4 patients had a recurrence in 3 months Therefore, this treatment seemed to be no better than other types in preventing recurrences

We published the early results The newspaper and radio fraternity, who incidentally, suffer notoriously from peptic ulcers, took up the matter, and inflated it into a scientific achievement of the first order Patients queued in front of the laboratory Fortunately, I had to go to China, and I thought that was a way out of an embarassing situation, but whether it was in San Francisco, or Shanghai, or Chungking the peptic ulcer patients were always there I relate this story as a warning against the risk of having one's work overpublicized It did, however, accomplish something It made available to us a large number of intractable cases of ulcer They seemed to have come out of hiding, hiding in despair They came from all quarters of the globe, and this has given us an opportunity to test the regimen in more than 200 ambulatory patients

In the usual plan the daily diet consists of protein hydrolysate and dextrimaltose dissolved in water, the total amount,

containing about 350 Gm of hydrolysate and about 500 Gm of the sugar, is divided into 8 equal feedings usually taken at 2 hour intervals at 8 00, 10 00, 12 00, 2 00, 4 00 6 00 8 00, and 10 00 If the pain recurs before the next feeding the intervals are shortened to 1½ or even 1 hour These feedings are continued for 2 weeks after the pain subsides In 95 per cent of the cases the patient is free of the pain after the first 24 to 48 hours On the fifteenth pain free day, the patient receives a bland breakfast (an unfried egg cereal and toast) followed by the hydrolysate-sugar feedings every 2 hours If there has been no pain, the patient receives supper (well boiled meat mashed potatoes toast, and ice cream) If the meals on this day caused no trouble the diet is extended to 3 meals on the following day, the sixteenth pain free day This together with 5 hydrolysate sugar feedings at intervals of 2 hours is continued for 2 months

I should like to emphasize that the details of these schedules were arrived at empirically and are subject to variation and improvement It may be that somewhat smaller amounts of hydrolysates will do It may be also that the treatment can be terminated in a month or should be extended to as long as 6 months

We have used three kinds of hydrolysates with similar results Some are better than others A patient unable to tolerate one may be switched to another hydrolysate

To what do we assign the improvement in these cases? We have thought of four possible explanations none of which is proved There is the fact that the hydrolysates being amino acids and peptides are amphoteric, and neutralize the hydrochloric acid We have shown that when 50 Gm of the hydrolysate mixture is added to gastric contents with a pH of about 2 4 the pH rises to 4 6 and stays that way for about 2 hours The administration of a highly nutritious substance may promote the repair of wounds This is also a possible explanation but very difficult to prove There is some indication

that a high blood level of amino acids may cause relaxation of pyloric spasm, since pain may be relieved by their intravenous injection, but the effect of amino acids on gastric and intestinal motility has not been established Then, there are the experiments indicating that amino acids may bind pepsin and thereby prevent its action Although this factor has not been studied sufficiently, it remains one of the possible explanations for the mode of action of the hydrolysates These are all merely suggestions They all may be incorrect.

From the practical standpoint, the course of peptic ulcer may be divided into three stages first, the stage of acute symptoms second, the stage in which symptoms have subsided but the ulcer has not healed, third, the stage in which the ulcer is healed There still remains the problem of recurrence We are quite sure of the efficacy of the treatment in the first stage, namely, the relief of the symptoms We do not know how effective it will prove to be in the prevention of recurrences We know of cases with premonitory symptoms of recurrence in which retreatment for a week checked the symptoms and prevented the recurrence Obviously, there are many unknown factors promoting the chronicity and recurrence of ulcers It is possible that a psychosomatic condition or a poor nutrition state may keep them from healing and that the cycle may be broken by correcting one or the other.

Dr Almy Are there any questions for Dr Co Tui?

Dr Seymour H Rinzler The taste of the amino acid digest is a practical problem How do you overcome it? Most of the materials on the market now have a very bad taste.

Dr Co Tui The taste of the hydrolysates is very unpleasant to the normal person, but, fortunately, from our point of view, a patient who has had ulcers for five or six years will take anything for relief The first 3 days are the most critical ones After that, patients may even get to like the material I wish to state that, in regard to the taste, some preparations are better than others.

Intern Do you make any provisions for vitamins during the period of 2 or 3 weeks in which the patients receive only the hydrolysate sugar feedings?

Dr Co Tui After the first week, we give a full complement of vitamins daily Recently, a patient developed swollen gums on the ninth day of treatment There was a suspicion of scurvy The swelling subsided after giving vitamin C

Dr Walter Modell Do all patients gain weight on the hydrolysate sugar diet?

Dr Co Tui Many do, about 50 per cent.

Dr Harry Gold Would not treatment by the intravenous route serve to distinguish the local from the systemic aspects of the therapy?

Dr Co Tui We are able to control the pain by intravenous injection However, it is almost impossible to administer the full caloric and nitrogen allotment of our hyperalimentation regimen by the intravenous route One has to give too much fluid

Dr Gold I wonder whether Dr Co Tui has any notion as to what part of the 40 Gm of nitrogen given to an average person in this regimen is really necessary That is what he happened to find satisfactory in early experiments and it is understandable that he has continued such doses Would it be safe to say that 20 Gm of nitrogen might conceivably do just as well, in which case one could give it by intravenous injection?

Dr Co Tui The neutralization of gastric acid with the amount of hydrolysate we use persists for about 2 hours With less, it will not last as long With the amount of feeding we give many patients still feel hungry so that our dose cannot be far above the critical one in most cases

Visitor Since Dr Co Tui feeds these patients large amou of protein hydrolysates with the idea of promoting healing the ulcer does he have any data on the blood protein levels b fore and after treatment?

Dr Co Tui We gave high protein feeding on a purely em

pirical basis and not because of an observed effect on the blood protein level You all know Charles Lamb s story of the Chinese boy whose house burned down, and with it his pig He touched the pig got his fingers scorched, then reflexly put his fingers in his mouth and found that the taste was good Thereafter, whenever he wanted to have roast pig he burned his house down There is in this an analogy to our treatment We found that 0 6 Gm of nitrogen did the work and we have continued to use it. We do know, however, that in about 20 per cent of the cases the blood proteins are at the lower limit of normal, about 5 8 Gm per 100 cc

Dr Modell In patients with peptic ulcer, is there any evidence that there is an inherent difficulty in absorbing or utilizing protein when given in its natural form and not as a hydrolysate?

Dr Co Tui We have no indication of that I should however, like to call attention to another point, namely, that in *patients with pyloric obstruction the hydrolysate relieves the* obstruction We studied 6 patients with partial obstruction, 3 with a complete obstruction through which not even water passed, and lately 2 additional patients with complete pyloric obstruction due to carcinoma of the pylorus In these the hydrolysate was able to pass when it was given in small doses, about 0 2 Gm of nitrogen per Kg, which is approximately what we take normally in a high protein diet It was an amazing experience We may be certain that in many cases of pyloric obstruction with an organic lesion super added spasm also may play an important rôle Hydrolysate feedings provide us with a new management of pyloric obstruction I mention this to support the view that the amino acid mixture imposes less of a digestive strain on the gastrointestinal tract than natural food Here are patients in whom even milk would be rejected but amino acids are allowed to pass

Dr Almy The usual diets for ulcer are notoriously low in proteins At a time when we were complaining that the diet

of the American prisoner of the Japanese contained only 45 Gm. of protein, I calculated that our standard hourly milk-and-cream feedings provided the ulcer patient with only 35 Gm. of protein a day.

I wonder what Dr. Weintraub has to say about Dr. Co Tui's plan of treatment. We have not yet heard from a radiologist.

Dr. Sydney Weintraub: I was the medical man proposing surgery for ulcer in the symposium held a few years ago to which Dr. Almy referred. It was there that Dr. Co Tui described his method. I have had no personal experience with it.

Some years ago, I examined the literature and found some remarkable figures. No matter what type of treatment was used, whether it was bed rest with the Sippy treatment, or ambulatory treatment, or whether it was feeding by tube, the results were about the same. At the end of the first year, there was 80 per cent of cures, if the term cure may be used; at the end of the second year it fell to 60 per cent; after the third it was 50; after the fourth, 30; and at the fifth year it leveled off at 20 per cent. There was, therefore, a 20 per cent cure in ulcer, no matter what method, before the introduction of Dr. Co Tui's treatment.

Next, I should like to say a few words about how to judge a remission or a cure in a case of peptic ulcer. First, there are the symptoms; the patient states there is no more pain, he feels fine, and he is putting on weight. Then, there are the X-ray findings, the disappearance of the niche. In a great many of these cases which are reported as cured by one or another of these criteria, one finds that they are not cured at all. We have had cases in the hospital in which the patient stated he felt well and wanted to go home, but the X-ray showed that the niche had actually grown larger. We have operated upon such cases and have found a chronic ulcer stuck to the pancreas. On the other hand, we had 2 cases in whom the niche had practically disappeared, which would make one believe that the patients

were cured The operation then showed that we had been misled, carcinoma had developed in the ulcer

Dr Co Tui has displayed very nice films showing the reduction in the size of the ulcer I should mention that that occurs with any kind of treatment We treated large numbers of patients with ulcer at the former Cornell clinic They were mostly ambulant, we hospitalized not more than 1 per cent of them They were all working people and had difficulty in pursuing a rigid diet In spite of these unfavorable conditions, the niches disappeared in about 95 per cent of them, and did so in a very short time In the average peptic ulcer, the niche dis appears in about 2 weeks I doubt if this can be accomplished any faster The rapid subsidence of symptoms and disappearance of the niche after Dr Co Tui s treatment seemed to me much like all of our past experiences with other treatments I believe that Dr Co Tui will have discovered something when he can report to us five years later that the curve of recurrences has been materially altered

Perhaps you will be interested in a story of a single case which we reviewed recently at one of our follow up conferences I mention it here because in examining the chart, my eye caught the name of Dr Co Tui The patient previously was admitted to this hospital for gastric ulcer, and was dis charged improved after 11 days, the treatment to be continued by a private physician Eight months later, he was readmitted for recurrence of his symptoms The history in the interval between these two admissions contained an account of treatments by various doctors in addition to a course of treatment by Dr. Co Tui s method On that regimen there was diarrhea for 3 days at the start, the treatment was pursued for 15 days during which time the patient improved symptomatically and gained 8 pounds Then, at the patient s request, three meals a day were added to the regular Co Tui regimen Promptly, the patient began to experience distress with his meals X ray examination ruled out gallbladder disease and duodenal ulcer

The patient abandoned this treatment and again consulted various doctors before returning to us for the present admission

The X rays were very interesting On the first admission there was the large, broad based ulcer which we reported as a benign ulcer In the second plate, after the course of treatment by Co Tui s method and others, an ulcer was still present The third plate showed marked diminution in the size of the lesion Gastroscopy failed to reveal any lesion Nevertheless, symptoms persisted, and so the patient was operated upon and the area resected Although the lesion appeared to be a benign ulcer on gross examination, the sections showed carcinomatous changes This type of case gives us a good deal of concern, and we are reluctant to temporize with medical treatment because of such experiences I think this person is going to get well, because the resection was made early

I would like to close this discussion by quoting Dr Walter Palmer, of Chicago In a chapter called The Therapeutic Fallacy," he states as follows ' For any chronic disease like peptic ulcer, the course of which is characterized by remissions and exacerbations the evaluation of therapy is difficult The cures for ulcer are legion, and most of them will be discarded as their predecessors have been The annual crop of new cures is due to many factors, one, prevailing methods of treatment are not completely satisfactory, two, the periodicity of the disease leads to false evaluation of the efficacy of the therapy under consideration, three, the factor of mental suggestion enhanced by the enthusiasm of the physician is extremely important yet difficult to assay, four, and last, the physician and the patient both succumb to the lure of new fads properly advertised.'

Dr Almy I think we all ought to consider the fact that Dr Co Tui predicted he would have relapses and was careful to say at least two years ago that the treatment should not be expected to do anything more than produce the first phase of healing

Dr Moore, would you care to comment on the application of these facts to surgical management?

Dr Samuel W Moore I think it is perfectly true, as has been brought out in this conference, that in the past we have starved these patients There has been a tendency to give nothing by mouth, and no protein I share Dr Co Tui s view that these patients should receive protein I also want to re-emphasize Dr Weintraub s statement about the periodicity of these ulcers Practically all of them can be healed very quickly with medical treatment, but they recur and the patients return to the clinic. When we think of peptic ulcers, we should differentiate between ulcers of the duodenum and ulcers of the stomach An ulcer in the duodenum practically never turns into carcinoma, whereas, in the case of the stomach, it is a matter of great uncertainty whether it is an ulcer or a carcinoma The doubt often fails to be resolved after repeated gastrointestinal series and gastric analyses One cannot be certain of it even at operation It is my firm belief, as well as Dr. Weintraub s, that, if an ulcer of the stomach fails to heal promptly with medical treatment, an exploratory laparotomy should be performed, and if there is anything in the stomach, it should be resected

Dr Modell I should like to ask about the use of Co Tui's diet in bleeding ulcers Is it continued then, and is the routine the same?

Dr Co Tui Yes it is and the results are good

Dr Almy I think that the chief objection to feeding in the case of bleeding ulcers is that one might have to operate at any time on such a patient. Does not the liquid food overcome that objection to some degree?

Dr Co Tui Yes the stomach is empty within an hour and one-half after a feeding Just omit one feeding and send the patient to the operating room

Dr Weintraub s case is matched by another we had at the French Hospital The patient had a gastric lesion We were

warned by the X-ray report that it might be a carcinoma. The patient felt so well after treatment and gained weight so quickly that both he and his doctor thought he was well. He returned in 6 months with an inoperable carcinoma. It is an important point which I failed to mention in the earlier part of my remarks, that one must differentiate between peptic ulcer of the duodenum and the stomach. As to the comparison of the results of our method with those of other methods, I should point out again that we applied our treatment only to intractable cases, cases which failed to respond to other methods. Otherwise, our results would have little meaning.

Visitor: Is peptic ulcer especially common in countries in which there is nitrogen starvation?

Dr. Co Tui: There seems to have been an increase in China. Peptic ulcer was a fairly infrequent occurrence among the Chinese. During the war, malnutrition, air raids, and other war worries played a part in the increase. I don't know which one of those factors has brought it about. I am not trying to blame protein deficiency for the production of peptic ulcers, but it is quite possible that protein deficiency prolongs peptic ulcers, and prevents them from healing.

Dr. Kirby A. Martin: Could we ask Dr. Co Tui how he selects his cases for this type of treatment?

Dr. Co Tui: Our original series were intractable cases. We went to the medical wards where we had patients in bed on a course of Sippy treatment. When they failed to respond to it after 3 weeks, we took them over. Our ambulatory cases usually had a history of from 3 weeks to 3 months of ambulatory treatment outside, which had failed to control their symptoms; it was then that we took them over.

Dr. Weintraub: What are your results with the marginal ulcers?

Dr. Co Tui: At first we thought they were very good. I don't think they are good at all now.

Dr. Weintraub mentioned the matter of suggestion in the

treatment of peptic ulcer I think it has to be considered, but we must not give it too much weight The fact that a patient may take one hydrolysate with improvement, and another without any, to some extent helps to rule out suggestion as a cause of the response.

Dr Gold I wonder whether Dr Co Tui has had any experience with the yeast hydrolysates There is a material made by Marvin R Thompson, which seems to me to be quite palatable

Dr Co Tui That reminds me of the subject of preparations The market will be flooded with these products, some good and some bad A hydrolysate which is not well prepared can cause more harm than the natural food I would suggest that we confine our work to only those products which have been shown to be efficacious There is a hydrolysate made from yeast, which is now provided by various companies, among them Marvin R Thompson I have tested it in two cases One responded well, and one did not. It is too early to say much about it.

There are three products which we are now testing all acceptable and all having good points These are the casein hydrolysate of E R Squibb and Sons, the protolysate of Mead Johnson and Company, and the lactalbumin distributed by the National Drug Company With these three, we have been able to keep our patients fairly happy In most cases, when one is rejected, another may be taken without difficulty I don't know why that is

Dr Gold There is a preparation manufactured by J. B Roerig & Comany, called Lactenz. It is the most palatable hydrolysate I have tasted

Dr McKeen Cattell Are there any side reactions?

Dr Co Tui Yes, there are side reactions The worst one is nausea Some patients just can't take the preparation We try to get around that by making up the sugar in one solution and the hydrolysate in another. The hydrolysate is made up in

as small a quantity as possible, and chilled They gulp it down and follow it with the dextrimaltose With that kind of treatment we have been able to reduce the number of reactions Other symptoms may be flatulence, distention, and diarrhea. Diarrhea is a very prominent one that we control by changing the product. For diarrhea we formerly used amphojel in 1 or 2 tablespoonful doses, now we use kaolin or kaopectin in tablespoonful doses This usually controls diarrhea Flatulence may be controlled by shifting from the dextrimaltose to lactose, and where it cannot be controlled that way, we give charcoal with it We have lately observed such reactions as palpitation, flushing, and dizziness They may not be caused by every batch of the product, they may be due to histamine or a histaminoid substance

SUMMARY

Dr Gold The discussion this afternoon centered chiefly on the value of a new method for the treatment of peptic ulcer, based on the viewpoint that a defect in protein metabolism may be a major factor in promoting peptic ulcer and preventing its healing The essentials of the method consist in the administration of a high caloric diet representing for the average adult about 350 Gm of predigested protein in the form of a protein hydrolysate, together with approximately 500 Gm of sugar, providing a total of about 3 500 calories daily The utility of this method was discovered accidentally in the course of the preoperative preparation of patients with intractable ulcer The rapid disappearance of symptoms and apparent healing of the ulcer as shown by X ray led to a more extensive trial Several other advantages of the method have been pointed out, namely, the fact that this diet seems to relax pyloric spasm and is therefore applicable to cases with what appears to be complete obstruction, and that it may be used in patients with bleeding ulcer, since the fluid diet leaving the intestinal tract very quickly, does not interfere with opera

tion should this become necessary The details of the protein hydrolysate–sugar feedings were outlined

The choice of protein hydrolysate preparations seems to be a matter of considerable importance, some being not only more palatable than others, but also more effective from the therapeutic standpoint

The precise manner by which this diet brings about these results has not been established Several theories have been ad vanced There is the possibility that it acts in part as an antacid, although there is indication that it may possess other actions as well, both local and systemic The method is not free of disagreeable reactions, partly due to the unpleasant taste and local actions of the protein hydrolysates, and partly the result of systemic side actions

As might have been expected claims for a new method for the treatment of peptic ulcer would not go unchallenged, and so it has been pointed out that the superiority of this method is far from proved, that most of the older methods relieve pain just as quickly and promote the healing of the niche, as shown by X ray, in much the same way That hyperalimentation with protein hydrolysates does not prevent recurrences has already been observed, but whether it will reduce the frequency and numbers of recurrences remains to be seen, and the issue con cerning the superiority of this method revolves around this point Special emphasis was placed on the fact that the striking results with this new method were obtained in patients who had failed to respond to the older methods of treatment.

The discussion brought out several additional points of interest, which one cannot afford to forget, namely, the fact that symptoms of ulcer may subside while the ulcer niche continues to enlarge and conversely, that the size of the niche may di minish, which suggests healing, while the symptoms persist. The desirability of surgical exploration in the latter cases was emphasized, especially in cases with gastric ulcer, since in these there is always the danger of carcinomatous degeneration

Treatment of Pneumonia

Dr. Walsh McDermott: This afternoon's conference will be on the management of pneumonia. The discussion will be opened by Dr. Tompsett.

Dr. Ralph R. Tompsett: The therapeutic aims in the treatment of pneumonia are: first, to control the infection, second, to promote the patient's comfort, and third, to manage or, if possible, prevent the development of irreversible anatomical or physiological changes during the period required for the control of the infection. Accomplishment of these aims requires the use of specific antimicrobial agents chosen on the basis of the etiology of the disease in the particular patient, and certain ge [illegible]
regardless of e [illegible]
general measures be neglected. The need for many of the general measures, however, is considerably reduced in those forms of pneumonia for which potent antimicrobial agents are available.

The most successful use of penicillin, streptomycin, and sulfonamides in pneumonia requires accurate bacteriologic diagnosis. Consideration of the present situation, however, makes it quite evident that the physician must do a great deal of work to discover a relatively few cases for which potent antimicrobial agents other than penicillin are available. As you know, probably over 95 per cent of all the patients with primary pneumonia will be found to have either pneumococcal pneumonia or primary atypical pneumonia. If penicillin is given to all of these patients purely on the basis of the diag-

nosis of pneumonia without regard to etiology then most of the patients will be receiving as effective an antimicrobial agent as is available Some of them who have primary atypical pneumonia will not be helped by the drug but very little if any harm will be done

Thus the efforts made to arrive at a precise bacteriologic diagnosis are directed toward the detection of a relatively small number of cases the most important of which are those caused by Friedlander s bacillus and the tubercle bacillus It is important that these be detected early because the serious damage which may occur within a short time may often be prevented by correct therapy

In pneumococcal pneumonia which is the commonest form aside from those occurring in epidemics the most effective agent for the control of the infection is penicillin The dosage of penicillin generally employed is approximately 20 000 units dissolved in 1 cc. of saline solution given intramuscularly every 3 hours Larger doses may be used if it is desired to lengthen the interval between injections Equally satisfactory results may be obtained by the use of penicillin orally in doses of 100 000 units every 2 hours

A variety of vehicles have been proposed for the administration of penicillin in an attempt to delay its absorption and thus obviate the necessity for repeated injections One preparation the Romansky formula of penicillin in oil and bees wax has received extensive clinical trial With this preparation it is possible to treat patients with pneumococcal pneumonia using only 1 or 2 daily injections of 300 000 units of penicillin Recently liquid preparations of this material have become available and these have done away with some of the disadvantages of the earlier preparations

Therapy of pneumococcal pneumonia by any of these regimens should be continued for a minimum of 7 days and preferably for 10 days With this treatment many patients with pneumococcal pneumonia may be expected to have a crisis

within 24 hours, and the vast majority within 48 hours In the remainder of the uncomplicated cases, by the end of the 48 hour period there will be definite evidence of improvement but the defervescence may be less abrupt In some, after this initial priod of defervescence, there follows a period of secondary low grade daily fever which may persist for as long as a week, although not accompanied by other evidence of toxemia Failure to obtain a response to penicillin therapy in the form *of one or another of the patterns which I have described constitutes* strong evidence that some complication is present, or that the pneumonia is not caused by pneumococcus

The various methods of administration of penicillin, which I have mentioned, have been notably satisfactory in pneumonia *All of them involve an attempt to maintain* continuously effective antimicrobial concentrations of penicillin in the body Although this is known to be very effective, it has also been shown that it is not necessary to maintain continuously high concentrations The studies of Tillett and his associates have shown that satisfactory results may be obtained in the treatment of penumococcal pneumonia with the use of doses of only 10,000 to 25,000 units of penicillin in saline given 3 or 4 times a day It was further shown by these workers that equally satisfactory results were obtained when some of the intervals between doses were 12 to 16 hours Other clinical studies have shown satisfactory results with dosage regimens which could not possibly have maintained what have been considered *'therapeutic levels ' for more than 12 to 15 hours* in each day During the past 7 months we have treated 26 patients with pneumococcal pneumonia, employing injections of aqueous solutions of penicillin, 300,000 units each, at intervals of 12 to 24 hours It has been our practice to give a dose of 300,000 units as soon as the diagnosis is made Then the patient is given 300,000 units at 8 A M and 8 P M until it is seen that defervescence is occurring At this point the regimen is changed *to only one injection* of 300,000 units a day,

at 8 A M The results in these 26 cases, as judged by all the usual criteria, have been identical with those of other treatment regimens

There are two other forms of pneumonia in which the same principles of penicillin therapy are applicable These are streptococcal and staphylococcal pneumonia It is possible that streptococcal pneumonia occurs fairly frequently in a mild form following pharyngitis, and if so, it closely resembles atypical pneumonia This is not the same entity as the well known streptococcal pneumonia, in which there is a widespread involvement of the lung with all the manifestations of a severe infection and rapid development of empyema, bacteremia, and metastatic abscesses It appears that satisfactory results may be anticipated in this severe form of streptococcal pneumonia with the use of penicillin, provided therapy is instituted early enough and before irreversible anatomical or physiological changes have occurred In these cases, it may be well to use the agent in dosage 2 or 3 times as high as that used in pneumococcal pneumonia

Staphylococcal pneumonia is also rare Most of the experience has been gained in those cases which occur in association with epidemics of influenza The same general principles apply as with streptococcal pneumonia The penicillin dosage should be even larger, for although many strains of staphylococci are highly sensitive to penicillin, there is considerable variation among freshly isolated strains Virtually all cases, however, may be expected to be favorably influenced by large doses of penicillin

The second most frequent type among the bacterial pneumonias is that caused by Friedlander's bacillus Although these cases make up only a small proportion of all the pneumonias they constitute a particularly important group today because they are not influenced by penicillin, whereas they respond favorably to streptomycin and the sulfonamides The recognition of cases of Friedlander's pneumonia is made even

more important by the fact that all too frequently their progression is rapid, within a day or two of the time the patient presents himself to the physician, the stage of abscess formation is reached The experience with Friedlander's pneumonia indicates that the treatment of choice is the combined use of streptomycin and a sulfonamide The organisms are generally sensitive to streptomycin Many of the strains are also susceptible to the sulfonamides Despite the fact that in many of the cases treated with streptomycin alone, the results have been satisfactory, there is theoretical reason supported by many *in vitro* studies, that the combined use of the two drugs may prevent or postpone the emergence of organisms resistant to streptomycin The average dose of streptomycin is 40 mg per Kg per day, or about 2 Gm per day in the average patient, given in 3 or 4 fractions by intramuscular injection The usual dose of the sulfonamides is used, for example, 2 Gm of sulfadiazine as the initial oral dose, followed by 1 Gm every 4 hours

Another form of pneumonia, which may be of acute onset and which may very closely simulate the more usual varieties, is tuberculous pneumonia This may also progress rapidly to the stage of irreversible or incompletely reversible damage. Consequently, the early recognition of the etiology is of the utmost importance Here also, the early use of streptomycin offers the best possibility for the reversal of the inflammatory process The daily dosage of streptomycin is somewhat smaller than in the case of Friedlander s infection because the treatment is more prolonged

The general measures namely, those of keeping the patient at rest during the acute phase of the pneumonia, relief of pain with codeine or morphine and the use of oxygen therapy may all be necessary They have less importance in those cases in which effective antimicrobial agents are available In some cases, such as the primary atypical pneumonias, they may be the only type of therapy available Such supportive measures

are very helpful in these cases as well as in other forms of pneumonia with complications, and in those who come under medical care only after the disease is in the advanced stage

Dr McDermott As Dr Tompsett said, the two important features in the management of pneumonia are the proper use of antimicrobial therapy and the institution of the general measures mentioned In most patients with bacterial pneumonia these general 'supportive measures are no longer of great importance In the other large group of pneumonias, identified by the clinical syndrome of primary atypical pneumonia the general measures may be of prime importance since no antimicrobial therapy is available

We are fortunate today in having with us Dr Frank Horsfall and Dr Harold Ginsberg of the Rockefeller Institute We promised that we would not call on them for any formal presentation, but they are available for questions I might start by asking them some questions on atypical pneumonia As you know however, these gentlemen have not limited their studies to atypical pneumonia and we may take advantage of their presence by questions on other aspects of pneumonia as well

Dr Horsfall I would like to ask you about a matter which is repeatedly discussed on the service Can one be sufficiently certain of the diagnosis of the clinical syndrome of primary atypical pneumonia to justify withholding antimicrobial therapy for, let us say, a 48 hour period or should all patients with an acute pneumonia receive antimicrobial therapy for a trial period with the view that the response will help to establish the diagnosis of atypical pneumonia?

Dr Frank L Horsfall It would seem to me that in the large majority of patients with primary atypical pneumonia, a careful clinical examination including a white blood cell count, ought to make it possible to conclude that the disease is probably not bacterial pneumonia There is a fairly sharp difference between the majority of patients with primary atypical pneumonia and the majority of patients with bacterial pneu-

monia. Physicians who are accustomed to seeing pneumonia should, in the majority of instances, have no great difficulty in differentiating one from the other.

As to the second half of your question, if one is reasonably sure that the diagnosis is primary atypical pneumonia, it seems to me not only unnecessary, but indeed unwise practice, to give a therapeutic agent which has no effect on the disease, merely for the purposes of security.

Dr. Harry Gold: Would Dr. Tompsett state how he makes fairly certain that the pneumonia is the primary atypical variety? What are its diagnostic characteristics, and, especially, the decisive ones?

Dr. Tompsett: One can be fairly certain of the diagnosis of primary atypical pneumonia only by careful evaluation of several features of the disease in comparison with similar features of bacterial pneumonia. In primary atypical pneumonia, the onset is generally less acute and the symptoms less severe than at the same stage of bacterial pneumonia. Chest pain is less likely to be prominent. The cough may be distressing but is often not productive of much sputum, and the sputum is not likely to be bloody or rusty in the early stages. The white blood cell count is generally between 5,000 and 10,000 per mm^3, and although it may be higher, it rarely goes as high as one generally finds it in the bacterial pneumonias. Those are the chief features. It should be emphasized, in connection with the *white cell count, that patients with very severe bacterial pneumonia may not have a leukocytosis and may even have counts* below 5,000. These cases, however, are not the ones in which confusion arises.

Dr. McDermott: The notion has been advanced that the administration of antimicrobial therapy might prevent a so-called secondary infection in these cases. Has secondary infection been a problem in primary atypical pneumonia?

Dr. Horsfall: Secondary infections in primary atypical pneumonia are exceedingly rare. Their incidence is certainly not

greater than 1 in 200 When they occur, they can be recognized at once and that is not too late for successful antibacterial therapy To give 199 patients frequent injections in the hope of preventing bacterial infection in one, seems to me unnecessary and overzealous treatment

Dr McDermott I have never seen bacterial infections following the atypical pneumonias we encounter here

Dr Horsfall It does happen but it is rare

Dr McDermott Dr Tompsett said something about mild forms of bacterial pneumonia such as streptococcal pneumonia with which we are all familiar Such cases might resemble atypical pneumonia Have you any thoughts on that point?

Dr Horsfall I agree with what Dr Tompsett has said and indeed I will go one step further We have seen patients in whom we did not suspect bacterial pneumonia, but who on careful study proved to have had pneumococcal pneumonia The clinical findings the X ray, and even the leukocyte count strongly suggested that the infection was primary atypical pneumonia Finally, when all the serologic and other laboratory work was completed it became evident that it was not the correct diagnosis and that the patient actually had pneumococcal pneumonia, due to a specific type of pneumococcus, and showed a specific antibody response But this is a rare occurrence and such cases do not constitute a therapeutic problem because they are so mild

Dr McDermott That brings up another problem It is virtually impossible now to obtain diagnostic sera for the typing of pneumococci in sputum What do you think about the necessity or the clinical usefulness of typing sputum?

Dr Horsfall That is an exceedingly difficult question to answer and particularly difficult for me It would seem to me that there is little clinical usefulness in typing pneumococci at the present time Indeed some of the best clinics in this city, and in others carry out very effective therapeutic regimens in

Dr. McDermott: Do you find the sedimentation rate of any value?

Dr. Ginsberg: I think that often the sedimentation rate is down to normal while they still have abnormal physical signs, and, in that case, I would not allow them unlimited activity.

Dr. McDermott: I take it that you allow these patients to be up and about when the fever has subsided even though they show rales of a particular type. Have you any idea why they tend to relapse if you allow them unlimited activity too soon?

Dr. Ginsberg: No. I am not even sure it is so, although it seems to be. What do you think, Dr. Horsfall?

Dr. Horsfall: I do not know of any evidence which proves that they relapse more frequently when they are allowed up in the presence of physical signs. Nonetheless, it seems to me wise to keep them in bed when signs are present.

Dr. McDermott: Dr. Muschenheim, would you agree with Dr. Tompsett's statement that tuberculous pneumonia can mimic an acute bacterial pneumonia, or the atypical pneumonia?

Dr. Carl Muschenheim: I think it is much more likely to mimic atypical pneumonia than bacterial pneumonia, particularly because the white blood cell count is so frequently normal or only slightly elevated in both atypical pneumonia and tuberculous pneumonia. In fact, I think one of the most difficult differential diagnoses in pneumonia is that between primary atypical pneumonia and tuberculous pneumonia. As Dr. Tompsett has pointed out, this differential diagnosis is of increasing importance now that we have an effective treatment for tuberculous pneumonia.

Dr. McDermott: Perhaps you are not as apt to use chemotherapy in those tuberculous pneumonias which resemble the atypical as in those which resemble the other bacterial forms. In other words, you might not want to give streptomycin immediately to a patient who had just a small patch of consolidation, whereas you probably would start streptomycin therapy

at once in the patient with involvement of an area as large as two thirds of a lobe or a whole lobe

Dr Muschenheim It is not uncommon in atypical pneumonia to have large areas of consolidation

Dr McDermott In the extensive tuberculous pneumonias that involve most or all of a lobe with an acute exudative process, how difficult is it to demonstrate tubercle bacilli in the sputum?

Dr Muschenheim Sometimes quite difficult I think most failures are occasioned by not looking for them right away So often this diagnosis is not even considered at first These cases are frequently confused with the other bacterial pneumonias and the correct diagnosis is not thought of until there *is a failure of response to penicillin or sulfonamide Then*, in other cases thought to be primary atypical pneumonia, tuberculosis is not considered until weeks have passed in which the presumed atypical pneumonia has failed to improve as anticipated

Dr McDermott It should be possible, then, to demonstrate tubercle bacilli readily?

Dr Muschenheim In the early stages one or two negative sputum examinations are sometimes obtained but one or two negative sputum examinations for acid fast bacilli certainly do not rule out the diagnosis

Dr McDermott I do not wish to ask all the questions Are there other questions now?

Dr McKeen Cattell I have one for you, Dr McDermott A year or two ago you accumulated some pretty convincing evidence showing that the high peak concentrations are not important in relation to penicillin therapy I am wondering *whether this new schedule of doses at 24 hour* intervals does violence to that idea?

Dr McDermott I think it is impossible to say, Dr Cattell, because no one really knows whether the high peaks of penicillin concentration above a certain point serve a useful pur-

pose It is suspected that they do not. One of the main reasons for suspecting this, is the notable efficacy of the penicillin beeswax preparations in which peaks are seldom obtained In evaluating the type of *intermittent therapy we have employed* one must consider two features of the penicillin concentrations First, the intramuscular administration of 300 000 units of aqueous penicillin produces a very high concentration of penicillin in the circulating blood within a few minutes second, it also results in the maintenance of penicillin concentrations above a certain minimum level for a fairly long period of time We believe that the 'effective concentration of penicillin in the body is not known It is generally assumed that in a particular infection there is a certain "effective concentration of penicillin at the site of infection Presumably, concen*trations below this are ineffectual, and increments above that* value are of no added benefit. Obviously, for successful therapy *in acute infections it is necessary to maintain* 'effective antimicrobial action for some period during each 24 hours The length of that period, whether it be 4 hours or 24 hours, probably depends on the speed with which that particular bacterial species multiplies and produces pathological changes Dr Tillett s work, which has been amply confirmed by numerous investigators, would indicate that in pneumococcal pneumonia, one has only to maintain the minimum detectable concentration of penicillin for about 6 hours out of the 24 and the regimen Dr Tompsett has been using provides just about that by a single injection of 300,000 units of aqueous penicillin daily

Dr Cattell What concentration do you regard as an effective one in pneumococcal pneumonia?

Dr McDermott We do not know We suspect that it is less *than the minimal detectable concentration* which is approximately 0 08 unit per cc of serum with the method of assay we use In staphylococcus infections, *the effective concentration* is higher

Dr Gold Do you regard a period of time below this presumed 'effective concentration' in the blood as an important feature in therapy? That is to say, do you aim to supply the drug in such a way as to provide, first, a high peak, then, a plateau of an "effective concentration,' and finally, a period below an effective concentration, as a means of making the organisms more amenable to reason?

Dr McDermott I do not think we can carry it quite that far, Dr Gold The original purpose of intermittent therapy was merely for convenience There is evidence in one particular infection that one form of humoral immunity to that infection is much less interfered with by intermittent therapy than by continuous therapy That observation may have no great significance in acute bacterial infections such as those caused by streptococci and pneumococci It would have considerable practical value if the same general principle prevailed in the more chronic infections, such as tuberculosis, syphilis, and staphylococcus infections In other words, it is at least possible that the development of acquired immunity might be less suppressed by intermittent than by continuous therapy That is an important question at the moment, but there is very little evidence available concerning it.

Dr Ginsberg One question comes to my mind along these lines Since we are looking for a convenient and efficacious agent which will maintain continuous blood levels perhaps it has been a mistake virtually to remove the sulfonamide group from the armamentarium of the physician It is practically not employed any more Perhaps it is considered old fashioned When properly used it is an effective agent, probably just as good as penicillin in pneumococcal and streptococcal pneumonia

Dr McDermott It is an effective antimicrobial agent, but I believe that the decline in its use is warranted The administration of aqueous penicillin is, after all, a fairly simple matter, as are also the more fluid preparations of penicillin in oil and

beeswax Another preparation, procaine penicillin which is now under investigation looks extremely promising indeed much more promising than penicillin in oil and beeswax provided it turns out to possess no significant toxicity I think we are right in abandoning sulfadiazine because of its toxicity and relatively low antimicrobial potency Do you agree with that, Dr Horsfall?

Dr Horsfall I do not disagree However, for the practitioner in the home, the use of a form of penicillin requiring injection is a serious problem This difficulty can be circumvented by increasing the dosage 5 fold and giving the material by mouth

Dr McDermott The use of sulfadiazine, as Dr Ginsberg suggested, might partially solve the problem of Friedlander's pneumonia All too often, cases of Friedlander's pneumonia admitted to the hospital go without a correct diagnosis during the first 48 hours despite the fact that we have every facility with which to make it, and that it is sufficiently publicized that such a condition exists The organism is a diplobacillus which can look very much like a pneumococcus if one is examining a sputum smear at three o clock in the morning I believe that the difference between an excellent recovery and a chronic illness is probably determined in that first 48 hours Would you agree to that?

Dr Horsfall Without any doubt

Dr McDermott During that period, too many of our patients receive penicillin therapy

Dr Walter Modell I think you have answered my question in part I want to know how you treat patients with pneumonia prior to making the specific diagnosis? How would you treat patients with pneumonia if you had no facilities for making a specific diagnosis?

Dr McDermott If we had absolutely no facilities for making a specific diagnosis and there were no prospects of such

within the next 48 hours, it would be undoubtedly safer to use sulfadiazine which, at least, might have some effect in Friedländer's pneumonia

Dr Modell How long would you wait before you added another drug?

Dr McDermott If you had more than one drug and no diagnostic facilities the thing to do would be to give both penicillin and sulfadiazine You would then be covering all the bacterial pneumonias except tuberculous This is, however, an extreme situation Despite the fact that we often talk of practicing medicine in isolated areas with no diagnostic facilities those areas are becoming pretty rare It is possible to obtain diagnostic facilities within a 72 hour period in most places

Intern We have seen patients with pneumonia caused by an organism susceptible to penicillin, but who do not seem to respond to penicillin therapy On examination, it does not appear that any complicating factors are present How long would you be willing to continue with penicillin alone, before concluding that it was ineffectual and that you had better switch to another drug like sulfadiazine?

Dr McDermott That is a general problem in the management of pneumonia namely that of the patient who apparently has a bacterial pneumonia and who has received an antimicrobial agent but is not improving satisfactorily Failure to respond usually is determined by the course during the second 24 hour period Certainly by the end of 48 hours, if the patient is just as ill as he was at the beginning, it is clearly apparent Almost invariably that situation is not the result of the fact that an organism of a species usually sensitive to the drug is, for some peculiar reasons not sensitive to it in that patient Generally, it is either not pneumonia or one has made the wrong etiologic diagnosis of the pneumonia For example, one may be treating Friedlander's pneumonia with penicil-

lin More commonly, in bacterial pneumonia there is present some complication of the pneumonia such as empyema or meningitis Would you agree with that, Dr Horsfall?

Dr Horsfall Yes, entirely

Dr Muschenheim In that connection, Dr McDermott it seems to me that the suppurative pneumonias are also ones which we have always to consider These are of increasing importance since the prognosis in bacterial pneumonias has improved so much An important problem in the differential diagnosis and management of pneumonia is that of making sure that there is no serious underlying primary disease like carcinoma or that it is not a suppurative pneumonia or an early lung abscess

Dr McDermott By "suppurative" pneumonia, do you mean a pneumonia breaking down into an abscess either because of the nature of the pneumonia or as a result of some anatomic distortion?

Dr Muschenheim It may be due to mixed infection

Dr McDermott Would you tell us how you think you can distinguish suppurative pneumonias?

Dr Muschenheim The response to treatment helps A suppurative pneumonia may respond with defervescence and clinical improvement, but the response may be only partial It is not necessarily a complication of a primary pneumonia It is a primary disease in which suppuration occurs such as the suppurative pneumonia so commonly associated with carcinoma

Dr McDermott We have been impressed with the fact that in cases of empyema complicating primary pneumonia penicillin makes the patient look and feel better There is some improvement, but conspicuous improvement does not occur until the empyema is discovered and drained Is that the case in suppurative pneumonias?

Dr Muschenheim Yes

Dr McDermott Dr Tompsett mentioned the antimicro-

bial therapy of streptococcal pneumonia, and we talked about mild forms Dr. Horsfall, have you any notion as to what we could accomplish with antimicrobial therapy today, if we were faced with a pandemic of streptococcal pneumonia of the sort that was seen during World War I?

Dr Horsfall That is a very important question I have heard it discussed by many people who had an opportunity to see hundreds of patients during World War I, and it is their belief that present antimicrobial therapy might fail because of the time factor A large proportion of patients who developed secondary bacterial penumonia during the pandemic had such fulminating disease that there would have been no opportunity for the administration of adequate antimicrobial therapy However, in those whose illness developed more slowly, I should think that the result might be exactly what one would expect now in primary bacterial pneumonias

Dr McDermott That brings us to another point that is disturbing me a great deal Many of the failures of current antimicrobial therapy in pneumococcal pneumonia are of that same type The patient comes into the hospital late in a state of cardiovascular collapse which resembles a state of shock He succumbs despite our best antimicrobial therapy, even though it is sufficient to inhibit bacterial growth to a point where one is unable to obtain a positive culture I am familiar with Dr. Stead s work which showed that the mechanism of that type of shock is different from the shock which occurs through blood loss or trauma and that there is no point in attempting to treat the shock of pneumonia as one would surgical shock. Have you any thoughts on that?

Dr Horsfall Yes I have We have treated, or attempted to treat, the peripheral vascular failure which so commonly precedes the fatal issue in pneumonia, and have employed the measures generally used in surgical shock In all honesty, we accomplished nothing but to hasten the fatal issue. Certainly, we were never able to reverse it

Dr McDermott You are referring to patients with a form of pneumonia which would be susceptible to antimicrobial treatment, provided you could reverse the shock That is a very important point We use antishock measures in these cases The available studies, including Dr Horsfall s own observations, however, indicate that they probably are of little or no value

Dr Gold I wonder whether we could hear a little more about procaine penicillin from Dr Tompsett It is an interesting material I recently saw a circular issued by Eli Lilly, stating that a suspension of this material in oil is now available on the market

Dr Tompsett I will be glad to tell what little I know about it Procaine penicillin is a crystalline salt formed from procaine hydrochloride and crystalline sodium penicillin G, which is relatively insoluble in water There are now several clinical investigations in progress The salt is put up in sesame oil or peanut oil, which are, as you know, easily administered fluid preparations It is thought that an insoluble salt of penicillin should be more slowly absorbed and, hence, provide more prolonged blood levels with a given amount of penicillin This particular preparation, by all the means we have for evaluating it, looks exceptionally good thus far As you know, a good preparation of penicillin in oil and beeswax will after a single dose of 300 000 units produce measurable blood levels for 18 hours in approximately 75 to 90 per cent of patients, and for 24 hours in about 50 or 60 per cent of patients Thus far, with a similar dose of procaine penicillin, 100 per cent of patients had measurable blood levels for 18 hours, 85 to 90 per cent, for 24 hours, approximately 60 per cent or more at 30 and 36 hours, and a significant number, for as long as 42 hours In rare instances, measurable levels persisted for 48 hours That for a single dose of 300,000 units looks good!

Dr McDermott What were the concentrations at 36 hours when penicillin was still measurable?

Dr. Tompsett: The concentrations were remarkably high for penicillin administered with an absorption delaying agent. Several were from 0 15 to 0.3 unit per cc.

Dr. McDermott: What would you think of the possibility of toxicity?

Dr. Tompsett: There are possibilities of toxicity. The amount of procaine in 300,000 units of procaine penicillin is 120 mg The toxicity of a single dose of 120 mg. is not great. That much, I believe, might even be given intravenously within a few minutes without very much danger. It would appear that the only real likelihood of difficulty would arise in those patients who are hypersensitive to procaine. This would not seem to constitute a very serious problem, but it should be kept in mind I wonder what Dr. Gold thinks about the toxicity of procaine?

Dr Gold I should think that such doses would be quite safe There are, of course, individual cases of unusual susceptibility to procaine, and every once in a while one hears of a disaster from a small dose which entered the circulation too quickly.

Visitor Is this cocaine or procaine?

Dr Gold It is even more true of cocaine, but I was speaking of procaine The safety of procaine as used by the anesthetists lies chiefly in the fact that it is given subcutaneously They seldom give procaine intramuscularly In the case of procaine penicillin, of course, one is injecting into the muscle, and that results in a situation of a different order from the standpoint of toxicity

Dr McDermott What do you think of the experience with the use of procaine in the treatment of peripheral vascular diseases? It has been given intravenously in doses of 1 mg. per Kg 2 or 3 times a week.

Dr Gold It is fairly safe there, and I think it is fairly safe in the case of the penicillin preparation. There are these isolated cases of hypersensitivity, but I doubt very much that

they ought to influence the use of material like this if it turns out to be an important form of therapy There is another point I should like to raise Would this procaine penicillin not do away with the intermittent aspect of treatment? I gained the impression that periods of subeffective concentrations of penicillin in a regimen of treatment may have some advantage

Dr McDermott Intermittent therapy might have advantages in some situations, but I do not think it has any advantage in the acute infections such as bacterial pneumonia.

Dr Ginsberg There is another possible complication in the use of procaine penicillin Do you have any idea how long it takes before the procaine is excreted?

Dr Tompsett No, as yet I do not have that information

Dr Ginsberg The point I am trying to make is that procaine is a sulfonamide inhibitor In the event that one should give it to a patient to whom one would later need to give sulfonamides, the latter drugs would have no effect until the procaine had disappeared, or until it had reached a very low concentration

Dr McDermott The procaine penicillin is absorbed over a period of 4 or 5 days If it is given daily for a long period, that could be a real problem

Dr Ginsberg It has been shown in patients given large doses of procaine for local anesthesia, that they may absorb enough procaine to cause their blood to develop antisulfonamide activity

Dr Modell How much sulfonamide does 1 mg of procaine inactivate?

Dr Horsfall About 1000 times as much or 1 Gm

Dr Cattell If the combination is absorbed very slowly, wouldn t the procaine absorption be spread out over a long period of time, just like that of the penicillin? Unless the combination has a special toxic property, we can assume that the procaine will be destroyed very quickly In an animal you can give half a fatal dose every 20 minutes with safety

Dr. McDermott That was Dr Tompsett's point. Even if the total amount used over a period of 10 days went into the circulation at one time, it would be less than a fatal dose I think Dr Gold s point is very well taken, however, that if a drug can produce a reaction one must think of the possibility of that reaction in connection with its administration

Visitor Would you comment on the use of penicillin aerosol?

Dr McDermott It has limited usefulness It is an effective way of treating pneumococcal pneumonia, but other methods are more convenient. The aerosol maintains effective concentrations of penicillin in the blood, but, on the whole, I believe that for practical purposes the other methods are superior

Intern I am wondering about the syndrome called "unresolved pneumonia, ' or the persistence of an X ray shadow after the patient apparently feels well in every way Do you believe there is such a thing as unresolved pneumonia?

Dr McDermott I suspect there is It is infrequent, but I suspect we will see more of it. The usual case called "unresolved pneumonia probably never was pneumonia, as you are obviously hinting It was tuberculosis or, perhaps, a carcinoma of the lung I do believe there is a small group of very elderly patients who would have died of pneumococcus pneumonia prior to the days of antimicrobial therapy, and who are being saved or whose illness is being converted into a chronic illness by the new therapy In some of these patients, resolution is incomplete and healing occurs by fibrosis Have you any ideas on that Dr Horsfall?

Dr Horsfall I think it will be seen occasionally in younger persons Already we have seen it in 2 persons under 30

Dr McDermott Were they patients who had been extremely ill?

Dr Horsfall Very ill indeed, and with extensive pneumonia There was no question about the diagnosis, and even

subsequent examinations by bronchoscopy revealed no adequate explanation for the unresolved pneumonia

Dr McDermott Is it your belief that these patients might not have survived prior to the advent of effective antimicrobial therapy?

Dr Horsfall Yes I am inclined to agree with you that it only occurs in the extremely ill

Dr Gold What proportion of the cases of pneumonia that come into the hospital now are primary atypical pneumonias?

Dr McDermott In our own service which is small it varies. During the winter, we may see a great deal of pneumococcal pneumonia and no atypical pneumonia Then we may have an outbreak of atypical pneumonia In our service that usually occurs in the late summer and fall I believe Dr Horsfall would know whether ayptical pneumonia tends to occur in outbreaks or whether there is a steady month by month incidence of it now

Dr Horsfall I think all the evidence suggests that the incidence is relatively constant far more so than that of bacterial pneumonia The incidence is somewhat lower in the summer than in the winter

Dr McDermott Is it the most common form of pneumonia?

Dr Horsfall At one military installation where all patients with a fever of 101° or more are screened because they must go through the station hospital there were in the last year more than 250 patients with pneumonia among a total population of about 6 000 Only 6 of these patients had bacterial pneumonia

Dr Gold The term virus penumonia has not been mentioned in this conference Practitioners use it freely To what does it apply?

Dr Tompsett The term primary atypical pneumonia is used to describe a clinical syndrome which is probably caused by a number of different etiologic agents Because it is sus

pected that most of these agents are viruses the term virus pneumonia has come into common usage It seems preferable however to avoid using the term virus pneumonia at least until the virus etiology has been established and then a more specific term should be available as has been the case in psittacosis

SUMMARY

Dr Tompsett The conference this afternoon has helped to crystallize some of the problems in the treatment of primary pneumonia which have arisen in connection with the development of the highly effective antimicrobial therapy namely, penicillin sulfadiazine and streptomycin After one has made a diagnosis of primary penumonia how important is it in these days to establish the causative agent? Is it safe to ignore the causative organism and proceed directly to treat with penicillin? It appears to be the consensus that the detection of the causative organism is still a matter of great importance If all the bacterial pneumonias were due to the pneumococcus the matter would be very simple because of the ease with which they can be controlled with an antimicrobial agent virtually without toxicity namely penicillin but these constitute only about 95 per cent of the bacterial pneumonias Most of the others include those due to streptococci staphylococci tubercle bacilli and Friedlander s bacilli Clinically these cases are often difficult to differentiate yet it is imperative to do so because their treatment differs Whereas pneumococcus pneumonia shows dramatic response within 24 to 48 hours after moderate doses of penicillin the streptococcus and staphylococcus pneumonias require much larger doses Special emphasis was laid on the problem of Friedlander s pneumonia This type does not respond to penicillin and is best treated by a combination of sulfadiazine and streptomycin In this disease irreversible changes may be produced within 48 hours so that a delay in appropriate therapy by a mistaken diagnosis may

prove disastrous The satisfactory response to streptomycin by cases of acute tuberculous pneumonia in the exudative stage adds further weight to the importance of the early recognition of the causative agent

A noteworthy feature of the discussion was the emphasis placed on the so-called primary atypical pneumonias sometimes referred to as ' virus ' pneumonias, due to as yet unidentified organisms some of which may be viruses While the incidence of primary atypical pneumonias is not established it is clear that they occur very frequently, and the indications are that their milder forms far exceed those of bacterial pneumonias These do not respond to any known antimicrobial agents, and their therapy consists essentially of supportive measures applied in relation to symptoms that arise

The discussion also embraced such items as the need for typing the pneumococcus, the place of the sulfa drugs in the treatment of pneumonias, the causes of failure to respond to therapy, and the various plans for the use of the antimicrobial agents It was pointed out that when sulfadiazine is necessary, 2 Gm may serve as the initial dose followed by 1 Gm every 4 hours In the case of streptomycin, the usual dose is from 20 to 40 mg per Kg daily, or about 1 to 2 Gm a day for the average adult by intramuscular injection in 3 or 4 fractions Interesting experience was related showing that the current schedules of intramuscular injection of penicillin at intervals of 3 to 4 hours in the treatment of pneumococcal pneumonia may no longer be necessary, and that equally satisfactory results may be obtained by the intramuscular injection of 300 000 units dissolved in 1 cc of saline and given at intervals of 12 to 24 hours The discussion also touched on a new penicillin compound, procaine penicillin, which, by virtue of the fact that it is insoluble, may pro[illegible] unusually s[illegible]ned high blood levels after a s[illegible] This is still [illegible] *mental stage.*

Treatment of Barbiturate Poisoning

Dr. McKeen Cattell: The statistics of the Medical Examiner's office in New York City show that next to carbon monoxide, the barbiturates are the most frequent sources of poisoning, both suicidal and accidental. We had a conference on the treatment of poisoning by the barbiturates about two years ago and we are to review this subject again this afternoon. There has been a great deal of interest in this type of poisoning because it is being encountered more and more frequently. It is a difficult form of therapy, requiring a good deal of judgment. We hope we can crystallize some information on the subject of the best procedures. Dr. Gold will open the discussion.

Dr. Harry Gold: From one point of view, patients with barbiturate poisoning fall into four groups, two which recover and two which do not. The first is the group of patients who recover without any treatment. All they require is general nursing The second is the group of patients who die regardless of how intensive and expert the treatment is. They have simply taken so large a dose that no antidote or method of treatment can save them. The third group embraces those patients who recover only because of expert management; without the most effective measures most effectively applied they would succumb. The fourth embraces those patients who die because of the treatment.

I have been in contact with a fair number of cases of barbiturate poisoning either through inquiries for advice or direct participation in their management. This experience impresses

me with the fact that there is great need for better understanding of the basic problems involved in the course of poisoning by this group of drugs as well as in the various aspects of its treatment.

I have here a few memoranda concerning such cases, which I just took out of my folder. Here is the case of the wife of a physician who is supposed to have taken 23 tablets of Nembutal at about 1:00 P.M. She was found in coma about an hour later. I first learned about this case 7 hours later when the physician called me for advice concerning the treatment and for a source of supply of picrotoxin. The only information that he had about her status was that she was in coma, that the blood pressure was 110, respiration 26, and heart rate 90. He had been looking after her from the beginning, but he did not know the state of her reflexes at the present time nor did he know how matters stood at the beginning, information which could be used as a basis for a decision as to whether the course in these 7 hours had been stationary, or progressing downward or upward. Such information would be of the utmost value in deciding the treatment. There was a period of 7 hours of management which passed by without yielding the slightest bit of the information that should have been obtained.

Here is another case: A few months ago I received a telephone call concerning a patient who took 21 grains of Sodium Alurate and 9 grains of Seconal. She went into deep coma, but now, 20 hours after the dose, she was alert and carrying on a conversation. The reason for the telephone call was that the patient looked somewhat flushed; and although all physical findings were normal, the physician was worried that the treatment might not have been adequate and that some additional measures should be taken to insure recovery.

Here is a memorandum about a 3-year-old child who had taken 19 grains of phenobarbital 24 hours previously. Although the stomach was washed within an hour after the dose, coma developed with respiratory depression. He was

given a total of 9 mg of picrotoxin by intravenous injection in 2 doses within a period of about 45 minutes this dosage being equivalent to about 45 mg for an adult It caused a prompt convulsion That apparently was not what they bargained for when they started to use picrotoxin, hence the long distance telephone call

These are a few fairly good samples of the type of problems that need to be explored and crystallized in relation to the treatment of barbiturate poisoning

Before any treatment is applied in a case of barbiturate poisoning satisfactory orientation is desirable regarding two questions First, how deep is the poisoning, and second, has the material been completely absorbed?

It is very helpful to know the amount of the drug the patient has taken but that information is frequently quite inaccurate, although it is well to have in mind that adults are practically certain to recover without specific treatment from oral doses of the order of 1 or 2 Gm of any of the commonly used barbiturates

I should like to recommend that the first thing one should do is to list on a sheet of paper the common guides to the depth of barbiturate poisoning state of consciousness, depth and rate of respiration blood pressure, heart rate, skin (warm, cold, wet, or dry) cyanosis pulmonary rales response to painful stimuli width of the pupils and reflexes (pupillary reactions knee jerks swallowing reflexes) One should indicate in a column the presence or absence of these signs by a plus or a zero Entries are then made on this form as time passes, at intervals of 15 minutes or longer depending on how severe the poisoning seems to be This provides a convenient record, easy to examine and interpret as a guide to the therapy Very often one decides to do nothing in a case when first seen because the barbiturate poisoning seems so mild but one reverses the decision after observation for a few hours because the knee jerk which was present has now disappeared, or the pupil which re-

acted to light has now ceased to do so, or the pupil which was first small has now become widely dilated, or the blood pressure which was at first 120/80 has now declined to 80/70 It is my experience that unless one makes a chart of this kind with these various specific points clearly listed, the chance is high that the record will be incomplete in some details essential for a decision regarding the treatment 2 or 3 hours later I cannot emphasize too strongly the fact that the type of treatment is often determined not by the state of the patient when first seen, but by the course which the poisoning has taken and that course is clearly revealed by a record such as I have outlined

Has the drug been completely absorbed? That is the next question which should be decided If one can be fairly certain of the answer to this question, the problem is much clearer It is one thing to assume that there is a great deal of the drug in the gastrointestinal tract and that deepening effects can be expected as the result of continued absorption It is quite another matter if one can be fairly certain that absorption is already substantially complete, and that the intensity of poisoning observed at the time is as great as the patient is likely to show There is also the question of washing the stomach In a paper by Fantus on the treatment of barbiturate poisoning in the *J A M A* (August 17, 1940), evacuation of the stomach is the first step advised in the case of a patient admitted to the hospital in coma What possible advantage could there be in washing the stomach in a case in which there is information that the poison was swallowed at least 20 hours previously? All one does in a case of that kind by washing the stomach is to expose the patient to the added danger of aspiration pneumonia It is true that one does not always know how long a period has elapsed since the drug was taken, but we should make use of the information in those cases in which one does know the approximate interval, and avoid useless and dangerous steps

In connection with absorption, it is well to have in mind the fact that the barbiturates are fairly rapidly absorbed A massive dose of a barbiturate given on an empty stomach can kill a cat in as short a period as 7 minutes Of course, if the barbiturate is taken shortly after a meal, the absorption is much slower There is also the fact that a massive dose of a barbiturate may cause such severe irritation of the stomach, with reflex closure of the pylorus, that absorption is delayed Taking all of these factors into consideration however, I believe it is proper to say that if several hours have elapsed since the drug was taken, one may safely assume that absorption is substantially complete and that little is to be gained by washing the stomach

By the same token it is safe to assume that if 6 or 8 hours have elapsed since the poison was swallowed, progressive deepening of the narcosis as the result of continued absorption is also unlikely Such a decision if based upon reasonably accurate facts, better defines the problem of therapy in the case in question For example if one encounters a patient in coma as the result of a barbiturate, but the condition is satisfactory in the sense that the pupils are small and react to light, the skin is warm, the respiration is fairly satisfactory, and the blood pressure is 110/70 and if this is the state at the end of 6 or 8 hours or longer following the dose and if there is no reason for suspecting interference with absorption, one would do well to withhold specific antidotes and apply only general nursing care, since such a patient is almost certain to recover I encountered a patient in such a state a few months ago The drug had been swallowed about 20 hours previously Although the general state was as I just described, the physician tried to restore consciousness by means of picrotoxin and Metrazol As I walked into the room I saw this apparently comatose patient suddenly kick his legs up into the air The patient was having picrotoxin fits This is precisely the type of patient I referred to in the first group, namely, those who do very well when they

are left alone, and whose lives are endangered by the use of analeptics

There is another point requiring orientation before therapy No single system can be depended upon to reveal the true intensity of the poisoning by the barbiturates There are of course, those patients in whom all systems seem profoundly depressed There are others, however, in whom one system may show fairly deep poisoning while another, fairly light For example, there are those in whom all of the common reflexes that can be tested are found to be absent, absent corneal and pupillary reflexes, absent knee jerks, absent swallowing reflex, etc , but the respiration is fairly normal and the blood pressure is satisfactory There are others in whom several of the reflexes are found intact but the respiration is so profoundly depressed that it seems unlikely they will go on very long without the secondary effects of anoxia There are still others in whom the respiration and reflexes reveal generally light narcosis but in whom the blood pressure is extremely depressed to a level of say 80/70 Clearly, the drug depresses the respiratory center more in one case, and the vasomotor center more in another case, and so on A thorough examination at the beginning will clearly reveal what system it is which requires specific attention in treatment

The secondary effects of anoxia must not be confused with primary poisoning Many patients with barbiturate poisoning, when first found, have been lying in a state of narcosis for several hours and there is a picture of advanced poisoning involving all the systems, which may be deceptive, because the deterioration is chiefly the secondary effect of anoxia rather than the primary effect of the drug itself As they lie there the tongue falls back against the palate or pharynx mucus collects in the bronchi, and together these factors so impair the respiratory exchange that a degree of poisoning is in evidence which seems to place the patient on the brink of disaster Some of these patients are relatively lightly narcotized, and the whole

picture is rapidly reversed by measures which improve the respiratory exchange Pull the tongue forward put in an air way, administer oxygen by nasal catheter, and remove the mucus from the upper part of the respiratory tree After this is done the patient begins to improve, and with such speed as to leave no doubt that the recovery bears no relationship to the elimination of the drug It is well to bear the factor of anoxia in mind because such patients being only lightly narcotized, are very susceptible to the analeptics Because of their profound depression, one sometimes judges that large doses of metrazol or picrotoxin are necessary One is then surprised to find that even a small dose produces a convulsion We should not be surprised about this when we bear in mind the fact that the appearance of the patient poisoned with barbiturate is often only in part the result of the direct depression by the drug and may in a large part be due to the secondary depression by the anoxia

In practically all current accounts of the treatment of barbiturate poisoning one finds the recommendation to use one or another of the analeptic drugs Metrazol, Coramine, or picrotoxin I think this is a mistake for a very large proportion of patients in coma as the result of a barbiturate recover without an analeptic Why not use them just the same and give the patient the added chance of recovering even if he would have recovered without it? The reason is that the analeptic is itself a source of danger when used in effective amounts I am not at all sure but that many patients are deprived of their chances of recovering by the too liberal use of these drugs Judgment as to which patient needs them and which patient is likely to do well without them is therefore decisive

Let us consider for a moment the patient with barbiturate poisoning in coma who seems fairly well from general appearances the color is good the skin is warm the blood pres sure is satisfactory, the pupillary reflexes are present, but the respiration is so slow and shallow that one has to strain to see

the patient breathe. Here the indication for immediate treatment is clear, namely, the use of a respiratory stimulant. Caffeine is the material of choice. It may be given in a dose of 0.5 Gm. of caffeine and sodium benzoate intramuscularly or intravenously. The dose may be repeated 2 or 3 times at intervals of 30 minutes, or more quickly in the case of the intravenous route in order to produce or to maintain an increase in the depth and speed of respiration. This may also be accomplished at times by inhalation of a mixture of oxygen and carbon dioxide. Caffeine has the advantage over some of the other analeptics for this specific purpose because it rarely produces secondary depression of respiration and there is little or no danger of overdosage producing convulsions.

In another case, the picture of poisoning may be similar to the one I just mentioned, but while breathing seems satisfactory the blood pressure is down nearly to a shock level of 80/70. Here, other types of stimulants are clearly indicated, namely, Neosynephrine or Paredrine. These may be given in doses of 10 or 20 mg. by intramuscular injection, and repeated as necessary at intervals of 30 minutes or longer. They frequently boost the blood pressure to more satisfactory levels and speed up the circulation. This may be all that is necessary in a case of this kind. By such measures a patient who is likely to get into serious difficulties by the secondary effects of vasomotor depression is lifted into a state in which recovery is insured. The point about such cases is that they are only lightly narcotized, only one system such as the vasomotor or the respiratory center being unduly depressed, endangering the patient's life by the secondary effects of its diminished activity.

Again, I advise against the use of convulsant analeptics like Metrazol or picrotoxin in such cases, because the dose of the barbiturate is apparently relatively small, and before a considerable amount of vasomotor or respiratory stimulation is

obtained with these agents one often finds oneself tangled up in the problem of managing convulsions

I have already referred to the fact that most descriptions of the treatment of barbiturate poisoning give one the impression that analeptic drugs should be used in every case in coma I believe that one of the most important aspects of treatment is the decision as to the kind of cases in which they should be withheld In laboratory experiments the evidence is fairly clear that animals may survive 2 to 3 times an otherwise fatal dose of a barbiturate when treated with picrotoxin Whether picrotoxin or Metrazol saves lives in humans however has not been very easy to determine Several years ago I looked into the matter and prepared a report for the Council on Pharmacy and Chemistry of the A M A We compared reports of cases in which the patients were treated with picrotoxin with those of control cases Authors concluded for example that picrotoxin was responsible for the survival of their patients after 5 and 6 Gm doses of phenobarbital but the literature revealed cases of survival from similar doses of phenobarbital without picrotoxin In the experience of the first 7 years with picrotoxin we found 26 cases of barbiturate poisoning with a mortality of 15 4 per cent but the literature showed control groups with a mortality of from 7 6 per cent to 25 per cent It is not easy therefore to make out an entirely satisfactory case for the use of the analeptics although the results of animal experiments might for the time being be taken as sufficient justification for their use

The case being what it is however makes it incumbent upon us to be certain that we do no harm with picrotoxin or the other convulsant analeptics and in order to avoid doing harm we should first make fairly certain that the patient is one who stands a fairly good chance of succumbing without the specific aid of an analeptic Here are a few general rules that are likely to be of some help Picrotoxin or other convul

sant analeptics should be withheld in all cases in which it is possible to elicit such reflexes as holding the breath or increased breathing by supraorbital pressure, pupillary reactions, and knee jerks These patients recover without picrotoxin If, as you observe the course, these reflexes begin to vanish, picrotoxin may be started Picrotoxin should be given to all patients in whom no reflexes can be elicited A patient who is in coma more than 40 hours after one of the rapidly acting barbiturates, such as Nembutal or Seconal, has almost certainly taken more than an ordinary lethal dose Such a patient should always receive picrotoxin

At this point, it might be well if I were to summarize the chief measures employed in barbiturate poisoning Obviously, in any given case, one uses only those which are indicated (1) Establish free respiratory exchange by pulling forward the tongue and the lower jaw, by inserting an airway and by suction of the mucus from the respiratory passages (2) Administer oxygen if there is cyanosis (3) Stimulate the respiration by caffeine if there is profound respiratory depression Attempt to raise the blood pressure by means of Paredrine or Neosynephrine if the blood pressure has reached dangerously low levels without evidence of secondary shock (4) Treat secondary shock by the usual measures infusions of plasma in quantities sufficient to raise the blood pressure to levels of 100 or more, or infusions of 5 per cent glucose in saline Maintain the water balance in the ensuing days by the intravenous injection of 2 or 3 liters of glucose in saline (5) Use picrotoxin as an analeptic if the conditons for its use exist (6) Treat with penicillin, 20 000 units intramuscularly every 3 hours, as a prophylactic against bronchopneumonia It is not infrequent that the patient recovers from the drug poisoning and, then, succumbs to a bronchopneumonia

Incidentally, one might also call attention to the need for observing the bladder When these patients are in coma they may fail to void and unless one is on the lookout for it, one

may be surprised by a large mass in the lower abdomen which may look like a 6 month pregnancy in a female associated with dribbling Such overdistention of the bladder is often damaging and leads to infection of the bladder

Dr Cattell The topic is now open for general discussion There are many questions which have been raised I have a number that I would like to ask Dr Gold Is there anyone in the back of the room who would like to start? I think Dr Gold we should have an outline of what would be your procedure in the cases in which picrotoxin is indicated Would you say a few words on that?

Dr Gold If one decides the patient should have picrotoxin the 0 3 per cent solution 3 mg per cc might be used Give about 10 mg of picrotoxin intravenously every 15 to 20 minutes If the veins are hard to get at one may use the same dose intramuscularly because the material is well absorbed from the muscle This dosage plan should be continued until there are signs of excitation in the form of flicking of the fingers grimaces or abrupt movements of a limb Sometimes the first sign of effective stimulation is obtained by the reaction of the patient to a painful stimulus such as supraorbital pressure Before the dose of picrotoxin the patient may have shown no reaction to this stimulus and no knee jerk after the dose the same stimulus (following a delay of several seconds) gives rise to slow movement of the limbs or body and an active knee jerk appears It is now necessary to maintain these states This may be done by intramuscular injections of similar doses at longer intervals the interval being determined by the length of time it takes for signs of excitation to vanish The reason for the intramuscular dose is that it avoids the high concentration immediately after the injection which sometimes precipitates a convulsion

Dr Cattell Dr Grace would you add anything to what Dr Gold said?

Dr William J Grace I have a few comments with regard to

the technical aspects If the veins are difficult to puncture, we usually set up an infusion and puncture the rubber tubing for each injection A method which has been used quite extensively is to give a sufficient quantity of picrotoxin every 30 minutes to produce some reaction As a guide to that we use the return of the corneal reflex or any reflex, and, in addition the tone of the muscle The patients are quite flaccid and if while the drug is being administered, one continually moves the arms or one of the extremities of the patient, one can feel some resistance in the extremities before any twitching or generalized convulsion is evident. We have used that method in our plan of the management

Dr Gold In relation to the matter of intervals for picrotoxin, it is well to bear in mind the point that picrotoxin in small doses develops its action rather slowly A dose of 2 mg of picrotoxin per Kg of body weight given intravenously in a cat, will produce a convulsion within 15 to 20 seconds Just about one round of the circulation and there it is A dose of 0 5 mg per Kg of body weight, on the other hand may require as long as 10 to 15 minutes to produce the convulsion Perhaps a wait of 30 minutes after each injection is not a bad plan to follow The point is that we want to elicit the full effects of one dose before we give the next dose in order to avoid overrunning The early doses are given at shorter intervals and the later doses at longer intervals

I should like to warn against the use of muscle tone as a guide to dosage In severe barbiturate poisoning picrotoxin produces sudden convulsive flicking of the limbs first The muscles may still be completely flaccid Resistance in the muscles develops after doses of picrotoxin too close to or well within the range of convulsant doses If you undertake to increase the tone of the muscles I am fairly sure that you will frequently overrun and find yourself with a problem of treating a violent convulsion

Visitor Would you care to discuss the treatment of the

convulsions produced by picrotoxin in barbiturate poisoning?

Dr Gold These convulsions can be controlled by small amounts of ether by inhalation They may also be controlled by an additional dose of barbiturate For that purpose it would be desirable to use a rapidly eliminated barbiturate like pentobarbital sodium or Pentothal Sodium A dose of 10 mg might be given intravenously to start with and increased as necessary until the convulsions cease The needle might be kept in the vein until the full necessary dose is given since the effect of any one dose comes on almost at once

Visitor Why should we worry about the fact that the analeptic whether it is picrotoxin or Metrazol or any other, may produce a convulsion in an overdose during the treatment of barbiturate poisoning? Is there any particular harm in the convulsion? I ask this because Metrazol is so commonly used for the specific purpose of producing convulsions in the treatment of schizophrenia

Dr Gold That seems to be a very proper question I am not certain that the convulsions are injurious In the study of this problem in the laboratory we obtained some evidence that convulsions may be injurious For example, in the case of cocaine it was found that a minimum lethal dose not only causes convulsions but death When such an animal was treated with barbiturates the convulsion was prevented and the animal survived When the dose of cocaine was increased by 50 per cent the treatment with the barbiturate still prevented the convulsion but the animal died just the same Cocaine therefore has a direct depressant action which seems to be augmented by the convulsions and when the convulsions are prevented the animal recovers from an otherwise fatal dose In such an experiment therefore, it seems that the convulsions are injurious

In our studies of strychnine poisoning in the laboratory, we observed another phenomenon A normal animal poisoned by

strychnine shows a rise in blood pressure with each convulsion When the animal receives a barbiturate, it requires much larger doses of strychnine to produce the convulsion With these larger doses of strychnine, a reaction appears which is not seen in the normal animal, namely, an initial rise of the blood pressure with a secondary fall to shock levels in association with each convulsion I do not know what the situation is in regard to picrotoxin or Metrazol, but we must be careful not to carry over the reactions to analeptics on the part of non narcotized patients to those that are under deep narcosis The patients poisoned with barbiturates require much larger doses of the analeptics than normal patients, and under those conditions reactions may be obtained which one never sees in normal people receiving the smaller convulsant doses In view of such experimental observations, it would seem to be wise to avoid producing convulsions by the analeptic drugs in barbiturate poisoning until there is more evidence that the convulsions under those conditions are not harmful You see we know a good deal about the reactions of the normal person to a convulsant dose of the analeptic, and of the normal person to a narcotizing dose of the barbiturate, but we are without sufficient information about the reactions of the patient poisoned by the combination of several times the fatal dose of both the barbiturate and the analeptic

Dr Walter Modell Why do you prefer picrotoxin to Metrazol, which, I think, works well in animals?

Dr Gold Metrazol is quite satisfactory but using several criteria of efficiency, the experiences in the laboratory tend to favor picrotoxin Metrazol has a somewhat shorter duration of action than picrotoxin, and this might necessitate more frequent doses in order to maintain the subconvulsive state I think these arguments are not very strong and I am not sure that the difference between these drugs is very important When we have Metrazol available, there is no need to go far out of our way to secure picrotoxin

Dr Janet Travell Would not Metrazol have an advantage in that its effects after intravenous injections are not delayed as in the case of picrotoxin?

Dr Gold That sounds like an advantage

Dr Travell You would not be so likely to overrun.

Dr Gold That is true

Dr Cattell A recent report by a group of British workers appeared in the *Journal of Pharmacology and Experimental Therapeutics*, in which a series of analeptics was investigated in relation to the time of recovery of mice from large doses of barbiturates Picrotoxin was found to stand way ahead of the others, and that is in line with the results of several other studies

Student If a person has been in coma a long time from a short acting barbiturate why give picrotoxin at all?

Dr Gold Are you referring to my statement that a patient poisoned by a short acting barbiturate, who is seen in coma 40 hours later, should be treated with picrotoxin?

Student Yes

Dr Gold The reason is that patients, poisoned by borderline fatal doses of the short acting barbiturates almost invariably regain some degree of consciousness within 24 to 36 hours If there is still deep coma at this time it is likely that they have had much more than the single lethal dose That, by definition, means that they will not recover without some help

Visitor Does picrotoxin or Metrazol merely enable a person to recover from an otherwise fatal dose of barbiturate or does it also increase the speed of recovery? If it also accelerates recovery, then it might seem wise to use these drugs even in cases in which it is likely that they will recover without the analeptic.

Dr Gold There is some evidence that animals recover from a barbiturate more quickly when treated with the analeptic than when allowed to recover spontaneously I am inclined,

however, to advise against their use merely to accelerate recovery because of the danger inherent in the use of large doses of these convulsant agents I believe that the possibilities for harm are greater than those for good

Intern Have you ever used strychnine for the treatment of barbiturate poisoning?

Dr Gold I have not used it myself in human cases but it has been used, and in doses of 2 mg or 1/30 grain subcutaneously at intervals of 1 or 2 hours Dr Travell and I published some papers several years ago on experiments with strychnine as an antidote to poisoning by alcohol and barbiturates Although it was possible to produce hyperexcitability and convulsions in the narcotized animals strychnine did not prove very effective in saving life There are other experimental studies in the literature which also rank strychnine fairly low down on the list of analeptics

Student What kind of supportive treatment do you give these patients who are in coma for many hours? You mentioned some of them being in coma as long as 40 hours or more

Dr Gold Supportive treatment is not very important in the first 24 hours or so, and it can be managed by intravenous infusions of 5 per cent glucose in saline It becomes of greater importance, however, when coma lasts much longer, 4 or 5 days, as is the case after massive doses of the barbiturates and after some of the long acting barbiturates In these cases supplementary measures might be helpful, such as plasma infusions and large doses of vitamin supplements It might also be well to consider the use of intravenous protein hydrolysates I do not know of any experience with the use of these in barbiturate poisoning

Dr Cattell In severe poisoning by the barbiturates the terminal picture is one of peripheral vascular failure. What do you think of the value of picrotoxin for improving the circulation by maintaining the central nervous system functions

at a higher level even though it does not affect the circulation directly?

Dr Gold I am inclined to think picrotoxin is of value against the circulatory depression through its action on the central nervous system

Dr Cattell You mentioned the use of epinephrine You did not state whether you would use that in severe poisoning

Dr Gold I mentioned Paredrine and Neosynephrine They are preferable to epinephrine because they are less apt to cause marked acceleration of heart and secondary vasodepres sion They are useful for raising the blood pressure in the milder cases of barbiturate poisoning with vasomotor depres sion These are patients in whom the color is fairly normal the skin is warm but the blood pressure is down to such levels as 80 or 70 systolic In such cases these drugs boost the pressure and accelerate the circulation

It is quite another matter however if the patient is in sec ondary shock In such an individual the blood pressure is apt to be very low the skin cold and clammy the neck veins col lapsed and the respiration profoundly depressed The pe ripheral constrictors are not apt to be of any value here These patients are to be treated in much the same way as any case of secondary shock with oxygen and plasma infusions in quan tities sufficient to raise the pressure to more satisfactory levels and to abolish the symptoms of circulatory collapse

Dr Modell I want to ask Dr Gold a question about the effect of picrotoxin on respiration Would you use picrotoxin if the respiration were seriously depressed but the other signs which you listed as indications for picrotoxin were not there?

Dr Gold In some cases I would There are always border line cases in which a decision is difficult to make There are instances in which the general picture is that of moderately deep narcosis from which one might expect the patient to re-cover without any specific treatment but the respiration is so depressed that one can hardly see the patient breathing Picro-

toxin might well be considered for such a case, but with the warning that this patient may only be lightly narcotized and may, therefore, be very sensitive to picrotoxin. The very fir dose may produce a fit.

Dr. Modell: The impression is that the analeptics are good respiratory stimulants. They are frequently used for that purpose alone.

Dr. Gold: Some of the analeptics are good respiratory stimulants. The case of picrotoxin presents special features. In the normal animal it produces respiratory stimulation at the dosage level which causes fits, but in the animal under the influence of large doses of barbiturates, it produces respiratory stimulation at a dosage level much below that which causes fits. The development of such a dosage differential is partly r sponsible for the usefulness of picrotoxin against depresse respiration in the narcotized individual.

Dr. Modell: Dr. Gold, you mentioned patients with barbiturate poisoning who succumb in spite of the most vigorous kind of treatment applied promptly and under the most favorable conditions. What seems to be the trouble in these cases?

Dr. Gold: I am not sure of the difficulty there. It looks as though none of the current treatment for barbiturate poisoning directly reverses the basic disturbances caused by barbiturates in the metabolism of the cells. In point of fact, we are not sure what that basic injury is. There are some studies which indicate that the barbiturates interfere with dehydrogenase activity, thereby blocking intermediary sugar metabolism. The oxidation of glucose, pyruvate, and lactate is impaired, but apparently not that of succinate. These observations have been put to the test, and there are suggestive indications that succinates may reverse barbiturate poisoning in animals. There is also the suggestion that sodium succinate given in an intravenous infusion of a 10 per cent solution in a dose of about 20 Gm. may be of some value in humans, but the

evidence is still far from satisfactory In any case, it seems likely that after massive doses of barbiturate some metabolic disturbance is produced which is irreversible by any of the current means of treatment Our present antidotal measures do not appear to function at the level of the specific mechanism of the cellular poisoning

Dr. Ephraim Shorr It is worth while pointing out that there is considerable doubt about the effectiveness of sodium succinate in barbiturate poisoning as well as about the way in which such benefit is achieved In our own laboratory, Furchgott and I have observed an enhancement of oxygen consumption of brain cortex with fairly large concentrations of succinic acid *in vitro* This effect, no matter what the concentration, lasts only 1 hour Furthermore, it achieves no increase in acetylcholine formation which would be expected from stimulation of brain metabolism by a normal substrate Experiments on a variety of other tissues under succinate stimulation have clearly demonstrated that succinate is unable to benefit any aspect of intermediary metabolism In fact it may actually depress the oxidation of normal substrates and thereby, interfere with normal metabolic processes However, there seems to be no doubt that in some instances the administration of sodium succinate has been of benefit in barbiturate poisoning as well as in experimental shock but the benefit seems to be attributable not to the succinate but to the sodium ion since equal benefit has been obtained from the administration of sodium bicarbonate Any state such as barbiturate poisoning, which leads to anoxia results in increased lactic acid in the blood and a fall in carbon dioxide combining power and blood pH The sodium ion in sufficient amounts would overcome acidosis and the deleterious effects associated with this condition The amount of sodium required to correct the acidosis should be determined by frequent estimations of carbon dioxide combining power

Dr Cattell I remember Dr Helpern mentioned the brain

lesion in the area of the globus pallidus in long lasting barbiturate poisoning similar to that of carbon monoxide If the injury proceeded that far, I do not think there would be much chance of recovery.

Dr. Gold. Yes, some of the irreversible poisonings by barbiturates probably involve this symmetrical necrosis of the globus in consequence of long lasting anoxia Others may develop the type of diffuse cerebral and cerebellar injury which we have seen in some of the animal experiments In one study, a barbiturate was found to produce permanent motor and postural changes associated with histological lesions in the brain. We do not know whether these also result from the sustained anoxia.

Dr. Travell· In view of these conditions, should not oxygen inhalation be considered under the heading of supportive treatment in barbiturate poisoning?

Dr. Gold· Yes, I believe oxygen should be used freely and especially, in those cases in which there seems to be the slightest question of inadequate respiratory exchange.

SUMMARY

Dr Gold· Cases of acute poisoning by the barbiturates are becoming more and more numerous The following measures for the treatment of acute barbiturate poisoning were explored in the conference this afternoon· establishment of a free airway, suction of mucus from the upper respiratory passages, oxygen inhalation, caffeine for respiratory stimulation, Paredrine and Neosynephrine for vasomotor stimulation, infusions of glucose in saline, infusions of plasma, vitamin supplements, prophylactic penicillin, and specific analeptics, such as Metrazol and picrotoxin.

The principles regulating the application of these measures were outlined, but emphasis was placed on the need for varying the procedures according to the indications of the particular case. It is often impossible to ascertain the precise dose of

barbiturate which the patient has taken The kind of treatment needs, therefore, to be decided on the basis of the depth of the narcosis and on the question of whether all the poison has already been absorbed Criteria for determining these two points were discussed Attention was called to the fact that a large proportion of the cases of barbiturate poisoning survive without specific antidotes, and to the fact that the use of the convulsant antidotes is not without danger A distinction needs to be drawn between depression due to the direct action of the drug and that due to the secondary effects of impaired respiratory exchange A patient profoundly depressed as the result of the anoxia may be very sensitive to picrotoxin and may develop a convulsion after a relatively small dose, while the patient similarly depressed as the result of a massive dose of the barbiturate may require several times the normal fatal dose of picrotoxin to produce stimulation Picrotoxin seems to be the antidote of choice The discussion attempted to crystallize the conditions under which it may be used and the most favorable plans for its administration

Therapeutic Uses of BAL

Dr McKeen Cattell BAL, or British anti lewisite is one of the most important developments which occurred as a result of the war in the field of drug therapy It has importance both from a practical and a theoretical standpoint I believe it is one of the very few instances of a drug which, developed according to pharmacologist s specifications has actually been found to work

Today, we propose to review the work of the pharmacologist and the clinician in relation to the therapeutic use of BAL Dr Chenoweth will start off with a brief account of the pharmacologic aspects

Dr Maynard B Chenoweth BAL has already achieved the status of Council acceptance The Council on Pharmacy and Chemistry of the American Medical Association has assigned a new name, dimercaprol which is a contraction of its chemical name, 2, 3 dimercaptopropanol Those who worked with it under the name of BAL, however, are likely to continue to call it that

It is an oily colorless liquid, poorly soluble and unstable in water It has a strong garlicky odor It is a dithiol derivative of glycerol, one of many dithiols synthesized and screened in recent years, and the one which offered the most promise for practical application in the treatment of arsenic poisoning

The search for a compound like BAL was based on the concept of the mechanism of poisoning by arsenic and other heavy metals It has long been known that trivalent arsenic in the case of the spirochete and human tissue as well blocks metab-

olism by combining with the -SH groups of enzyme systems The idea, therefore, was to provide a source of -SH groups which could compete with the tissue -SH groups for the arsenic Early experiments with monothiols, such as cysteine and glutathione, indicated that some such action could develop, but with these substances it was of a magnitude insufficient to produce a clinically useful effect The search was extended to other sources of SH groups, the dithiols BAL was one of the first of these to be examined and was found to possess the necessary properties It has been demonstrated that a competition for arsenic develops in the body between SH groups of tissue enzyme systems and the SH groups of BAL It has further been shown that these reactions are reversible, and the direction of the reaction is influenced by the presence of available SH groups from the one source or the other The effectiveness of a dithiol appears to be directly related to its ability to form a relatively stable heterocyclic ring containing the arsenic. Thus tissue -SH groups already in combination with arsenic can be made to release the metal when large enough doses of BAL are given, and the toxic action on cells may be counteracted even though some time has elapsed This indicates that BAL would be clinically useful even after symptoms of arsenic poisoning have developed It also indicates that treatment with BAL must be prolonged until the arsenic is eliminated so as to maintain a preponderance of SH groups derived from BAL. It should be remembered that although the chemical reaction of the tissue thiol radicals and arsenic is reversible, some of the effects of poisoning may be irreversible BAL cannot, therefore, be expected always to relieve all of the effects of arsenic poisoning This fact becomes increasingly important with the length of time after arsenic poisoning before the BAL treatment is started As a consequence of the liberation of arsenic from its combination with SH groups of the tissue enzyme systems and the formation of BAL bound arsenic, the arsenic level in the blood and the amount excreted

in the urine increase. Thus, not only are cells saved from poisoning by the arsenic in the body, but the poison is also eliminated from the body. This, then, is the basis for the use of BAL in the treatment of heavy metal poisoning.

This is not, however, the entire story. BAL produces disagreeable and toxic effects. In experimental animals, BAL produces a characteristic train of symptoms: Small doses cause blinking, blepharospasm, lacrimation, salivation, and conjunctival edema; larger doses, ataxia, urination, and respiratory stimulation; fatal doses, respiratory depression, pulmonary edema, and convulsions. In addition, there are some interesting effects on the cardiovascular system. There is a primary action on certain peripheral arterioles, a reversible constriction, which, after small doses, produces a rise in blood pressure, after larger doses, enough capillary damage to cause a fall in blood pressure and signs of peripheral vascular failure. The rise in peripheral resistance is marked in the limb vessels, but is not present in the arterioles of the liver or the splanchnic area. BAL also causes a rise of blood lactic acid and a lowering of blood pH and carbon dioxide combining power. These effects are produced by intravenous and intramuscular injection, and since the agent is absorbed from the surface of the skin, they are seen after cutaneous application when the dose and the area over which it is spread are large enough. BAL is rapidly eliminated by the experimental animal, and the effects of a nearly fatal dose may disappear in 5 or 6 hours. Toxic effects have been observed in humans who have received therapeutic doses of BAL, namely, paresthesias, sweating, a sense of warmth, pain (in limbs, jaws, abdomen, and head), lacrimation, blepharospasm, salivation, vomiting, unrest, apprehension, weakness, fatigue, acceleration of the heart, and a rise of both systolic and diastolic blood pressure. No serious consequences have been reported. These effects are usually produced by single doses greater than 3 mg. per Kg. Doses as large as 8 mg. per Kg. produce rather marked symptoms. The effects

come on quickly after intramuscular injection in a matter of a few minutes in some cases but last only an hour or two Doses of the order of 5 mg per kg have been given at intervals of 3 hours during the day without significant cumulation although individual doses have produced symptoms The usual dose prescribed for therapeutic effects is 2 5 to 3 mg per kg, this rarely produces significant discomforts It is generally given at 4 hour intervals to avoid the danger of cumulation

BAL is provided for therapeutic use in ampoules of 4 5 cc It is a 10 per cent solution of BAL in peanut oil together with 20 per cent benzyl benzoate which is used as a solubilizer It is injected intramuscularly It often causes some pain at the site of injection An ointment of BAL in petrolatum was developed during the war for local use after exposure to arsenical blister gases This is no longer available since the possibility of this type of exposure to arsenic is no longer a problem However it can be made up for local use in cases in which there is a reaction due to the local effect of arsenic In this connection it is well to remember that BAL may be absorbed from the surface of the skin and perhaps even more effectively through a denuded area such as may be present after local action of a metal

All of the spade work on animals and humans was carried out with arsenic Interest then turned to the possibility that the therapeutic action of BAL might also apply in case of poisoning by other heavy metals Investigation both in the laboratory and in the clinic has already indicated that the value of BAL does extend to poisoning by other metals Clinical experience exists showing that BAL is effective in the case of poisoning by gold and mercury There is experimental evidence for its value in the case of poisoning by antimony bismuth chromium and nickel but clinical support is still lacking Indifferent results have been obtained in experimental poisoning by thallium and silver while in the case of poisoning by lead and selenium matters seem to be made worse by BAL.

Dr. Cattell Dr Chenoweth, is it not true that the toxic symptoms of BAL which have been reported in humans are fairly evanescent?

Dr Chenoweth Yes, quite fleeting, a matter of an hour or so

Dr Cattell We are not alarmed by toxic symptoms in humans because, in experimental testing with larger doses of the compound than are used clinically, all symptoms subsided within a very short time

Perhaps we should leave further discussion until we hear what Dr Riker has to say about the clinical aspects of BAL.

Dr Walter F Riker, Jr Clinically, BAL has been most intensively studied in the treatment of arsenic poisoning especially in the treatment of reactions arising from antiluetic therapy

As already indicated BAL is available as a 10 per cent solution in peanut oil, solubilized with benzyl benzoate This solution is dispensed in ampoules containing 4 5 cc for intramuscular injection The symptoms which BAL may produce in humans have already been indicated Their occurrence depends largely on the size of the dose and the frequency with which it is given In a series of studies on normal men it was found that a dose of approximately 3 mg per Kg can be given before toxic symptoms appear As has been mentioned the reactions which occur from these and even larger doses are of minor importance since they are reversible and of short duration There have been no serious reactions complicating BAL therapy in man With a dose of 2 5 mg per Kg, the incidence of reactions after approximately 700 injections was less than 1 per cent, and these were of a minor character, consisting mainly of mucosal irritation BAL is fairly rapidly eliminated so that the danger of cumulation is small A study by Modell Gold and Cattell demonstrated in a series of patients that relatively large doses, 5 mg per Kg given at 3 hour intervals for 4 doses did not produce any cumulative effect

The BAL regimen in the treatment of arsenic poisoning is based largely on the toxicity studies in man Thus an intra muscular dose of 2 5 mg per Kg of BAL may be chosen for a mild case of poisoning and 4 to 6 such doses may be adminis tered every 4 hours for the first 2 days The same dose may be repeated once or twice daily from the third to the tenth day The courses of BAL will vary with the individual case but there is rarely need to administer the doses more frequently than every 4 hours In a severe case of poisoning it may be desirable to increase the dose to 3 or 4 mg per Kg despite the appearance of toxic symptoms from the BAL In the first 2 days this dose may be repeated every 4 hours until 6 such doses have been given and thereafter once or twice daily until the tenth day or until treatment is no longer required There is still insufficient clinical experience to decide the precise dose or duration of treatment in any particular case The member clinics of the Co-operative Clinical Group have used BAL in the treatment of complications arising from arsenotherapy The results obtained were correlated and evaluated by Drs Harry Eagle and Harold J Magnuson of the United States Public Health Service and the Johns Hopkins University The results in 55 cases of arsenical encephalopathy caused by in tensive Mapharsen therapy have been reported Of these 15 were considered mild cases without coma or convulsions In this group treatment was begun within 12 hours after the onset of symptoms All 15 recovered completely by the fourth day with an average of 2 5 days A total of 31 of the 55 cases classified as severe because of convulsions and coma were treated within an hour after the onset of symptoms Among these there were 24 complete recoveries and 7 deaths The average total dose of BAL used in these cases was somewhat larger than in the previous group and the time to complete recovery was an average of 4 days The remaining 9 cases were also of the severe type but in these treatment was delayed for 30 hours or longer after the onset of the symptoms The results

here were *much less impressive*, 5 of the 9 died, but I think that, without BAL treatment, the outcome is apt to be fatal in nearly all cases of arsenical encephalopathy in which coma convulsions, and high fever are present There were 88 cases of arsenical dermatitis treated with BAL. Among these 37 were of a mild form Treatment was begun in an average of about 10 days after the appearance of the rash, improvement was in evidence in an average of about 2 days and in about 5 days, *recovery was complete* Only 3 of the patients in this group failed to show any response to treatment There were 51 cases of the severe form of dermatitis the classical exfolia tive type In these, treatment was started in an average of about 16 days after the onset of symptoms In this group 41 showed distinct improvement in an average of about 3 days and complete recovery in 13 days The response to treatment was prompt, within 24 hours there was a fall in the tempera *ture, and the inflammatory reaction and edema* of the skin began to subside Experience with jaundice associated with arsenical therapy has not yet provided a definite answer as to the value of BAL In a group of 16 reported cases there were only 5 in whom BAL appeared to provide symptomatic relief The clinical recovery in these 5 seems to have been unusually rapid We had a patient in this hospital who developed jaun dice following arsenical therapy There was the question as to whether the jaundice was due to the arsenical treatment or to a coincidental infectious hepatitis We decided to try BAL and the results strongly suggested that it was beneficial the *icteric index declined from 95 to the* normal level after treat ment for 4 days and the patient was discharged from the hos pital, symptom free after 7 days the follow up in this patient showed no signs of recurrence of jaundice or *of liver disease* The course in our patient was similar to that in the 5 cases re ported by Eagle and Magnuson to which I have just referred The remainder of their 16 cases showed no clinical improve-ment on BAL therapy It may well be that the arsenic is not the

sole factor in the production of this type of jaundice, for if it were, the use of BAL should bring about rapid recovery because of the established interaction of BAL and arsenic BAL has been used in the treatment of blood dyscrasias resulting from arsenotherapy, but the experience is still too small for a satisfactory evaluation It appears to have been successful in granulocytopenia and agranulocytosis resulting from arsenic, but apparently unsuccessful in the arsenical aplastic anemia

In the treatment of poisoning by arsenic in man, the sooner BAL is given the better is the response There is fairly strong indication that the therapeutic response to BAL is related to the withdrawal of arsenic from the tissues The detection of increased excretion of arsenic in the urine is another matter Such an increase is frequently observed and the peak excretion occurs approximately 4 hours after the dose of BAL It is not always possible, however, to demonstrate an increase in the urinary excretion of arsenic sometimes as the result of the fact that the amounts due to BAL are too small to be detected in a 24-hour total excretion

BAL has proved very effective in the management of acute poisoning by bichloride of mercury The group working with Dr Longcope of the Johns Hopkins Hospital, in an early report presented an account of 42 cases of bichloride of mercury poisoning with doses varying from 0 5 to 20 Gm Among these, 37 made complete recoveries treatment with BAL having been instituted within 4 hours after the dose was swallowed Many of these patients were exceedingly ill when treatment was started Symptoms were relieved dramatically They compared a group of 86 patients with bichloride of mercury poisoning in whom various measures other than BAL were used, with a group of 24 cases in which the BAL treatment was used In both groups, the dose of bichloride of mercury was 1 Gm , and treatment was started within the first 4 hours Among those treated with BAL there were no fatalities, whereas in the control group 31 per cent succumbed

here were much less impressive; 5 of the 9 died, but I think that, without BAL treatment, the outcome is apt to be fatal in nearly all cases of arsenical encephalopathy in which coma, convulsions, and high fever are present. There were 88 cases of arsenical dermatitis treated with BAL. Among these, 37 were of a mild form. Treatment was begun in an average of about 10 days after the appearance of the rash; improvement was in evidence in an average of about 2 days; and in about 5 days, recovery was complete. Only 3 of the patients in this group failed to show any response to treatment. There were 51 cases of the severe form of dermatitis, the classical exfoliative type. In these, treatment was started in an average of about 16 days after the onset of symptoms. In this group, 41 showed distinct improvement in an average of about 3 days, and complete recovery in 13 days. The response to treatment was prompt; within 24 hours there was a fall in the temperature, and the inflammatory reaction and edema of the skin began to subside. Experience with jaundice associated with arsenical therapy has not yet provided a definite answer as to the value of BAL. In a group of 16 reported cases, there were only 5 in whom BAL appeared to provide symptomatic relief. The clinical recovery in these 5 seems to have been unusually rapid. We had a patient in this hospital who developed jaundice following arsenical therapy. There was the question as to whether the jaundice was due to the arsenical treatment or to a coincidental infectious hepatitis. We decided to try BAL, and the results strongly suggested that it was beneficial; the icteric index declined from 95 to the normal level after treatment for 4 days, and the patient was discharged from the hospital, symptom-free, after 7 days; the follow-up in this patient showed no signs of recurrence of jaundice or of liver disease. The course in our patient was similar to that in the 5 cases reported by Eagle and Magnuson to which I have just referred. The remainder of their 16 cases showed no clinical improvement on BAL therapy. It may well be that the arsenic is not the

sole factor in the production of this type of jaundice, for if it were, the use of BAL should bring about rapid recovery because of the established interaction of BAL and arsenic. BAL has been used in the treatment of blood dyscrasias resulting from arsenotherapy, but the experience is still too small for a satisfactory evaluation. It appears to have been successful in granulocytopenia and agranulocytosis resulting from arsenic, but apparently unsuccessful in the arsenical aplastic anemia.

In the treatment of poisoning by arsenic in man, the sooner BAL is given, the better is the response. There is fairly strong indication that the therapeutic response to BAL is related to the withdrawal of arsenic from the tissues. The detection of increased excretion of arsenic in the urine is another matter. Such an increase is frequently observed, and the peak excretion occurs approximately 4 hours after the dose of BAL. It is not always possible, however, to demonstrate an increase in the urinary excretion of arsenic, sometimes as the result of the fact that the amounts due to BAL are too small to be detected in a 24-hour total excretion.

BAL has proved very effective in the management of acute poisoning by bichloride of mercury. The group working with Dr. Longcope of the Johns Hopkins Hospital, in an early report, presented an account of 42 cases of bichloride of mercury poisoning with doses varying from 0.5 to 20 Gm. Among these, 37 made complete recoveries, treatment with BAL having been instituted within 4 hours after the dose was swallowed. Many of these patients were exceedingly ill when treatment was started. Symptoms were relieved dramatically. They compared a group of 86 patients with bichloride of mercury poisoning in whom various measures other than BAL were used, with a group of 24 cases in which the BAL treatment was used. In both groups, the dose of bichloride of mercury was 1 Gm., and treatment was started within the first 4 hours. Among those treated with BAL there were no fatalities, whereas in the control group 31 per cent succumbed.

Dr Cattell The subject is now open for general discussion Are there any questions?

Dr Harry Gold I should like to ask Dr Riker how he would explain the fact that BAL is so effective against arsenical poisoning, and yet, in some patients no increase in the excretion of arsenic in the urine is detected He stated that the increased excretion may be small and may occur in the form of a brief peak of excretion, and, therefore, escape detection in a 24 hour specimen of urine Is it likely that such a small increase in the excretion of arsenic could be responsible for the dramatic effects of BAL in controlling the situation in a case of arsenic poisoning?

Dr Riker We are not certain of the explanation It may be that this small increase in arsenic excretion is highly significant because it is arsenic released from combination with a vital organ or tissue There are other possibilities There is indication that BAL alters the distribution of arsenic between the urine and the feces, and an examination of the urine alone may fail to reveal the increased excretion of arsenic There is also the possibility that the arsenic removed from vital tissues and combined with BAL may circulate in an inactive form so that even though excretion is not accelerated, the combination is doing the patient no harm

Dr Chenoweth I should like to point out that the doses of BAL used in the studies of Dr Longcope and his group were as high as 7 mg per Kg in cases of acute poisoning by bichloride of mercury In spite of these large doses they observed no toxic symptoms of BAL This may be due to the fact that the large quantities of mercury present in these cases combined with the BAL and thereby prevented the toxic symptoms of BAL

Dr Cattell The mutual antagonism between BAL and metals is also seen in the case of arsenic Not only is BAL an antidote to arsenic, but it has been shown, under experimental conditions of arsenic poisoning that arsenic is an antidote to

BAL. In the presence of arsenic, animals are able to tolerate larger doses of BAL without showing toxic symptoms of the latter

In connection with the problem of therapeutic doses of BAL, it may be well to emphasize our experience in luetic patients who are not poisoned with arsenicals In these, intramuscular doses of 5 mg of BAL per Kg every 4 hours, and single doses as high as 8 mg per Kg were given without serious effects It is true that there were many disagreeable symptoms with such doses, but there were no effects which gave cause for alarm

Visitor Does BAL have any value in poisoning by gold?

Dr Riker *In vitro* experiments show that gold reacts with BAL to form a thio aurate There is no experimental work in animals that I know of, which shows that BAL is effective in poisoning by gold preparations There are, however, some recent clinical results suggesting a favorable effect of BAL in toxic reactions produced by chrysotherapy in arthritis

Visitor Which of the complications of chrysotherapy have been successfully treated by the use of BAL?

Dr Riker The dermatitis, both the exfoliative and seborrheic types, conjunctivitis ulcers of the palate, thrombopenic purpura and granulopenia have been reported as helped by BAL, but more experience is necessary for the final evaluations of BAL in all the manifestations of this type of metal poisoning

Visitor Could one confuse the reactions from BAL with those of the metal poisoning?

Dr Riker In general, the presence of metals such as arsenic mercury, or even gold appears as already indicated by Dr Cattell, to reduce the toxicity of BAL, and with the doses generally given in treatment, severe reactions from BAL are not to be anticipated I cannot think of symptoms due to BAL which may be confused with those due to one of the heavy metals. The picture produced by BAL is unique.

ily dissociated. Some of it may be fairly rapidly excreted, while the rest may be stored in the organism as a relatively innocuous complex. Either case results in protecting the body tissues against arsenic. There is evidence that in the animal, the insoluble complex circulates in a very small particulate form, possibly of a colloidal nature, and that it may be stored in the reticulo-endothelial system. There are cases of dermatitis resulting from a minute amount of arsenic, and it is believed that this may represent a hypersensitivity reaction. BAL has proved effective in this type of condition, a fact which suggests that the binding of a minute amount of arsenic with BAL is, in effect, equivalent to neutralizing an antigen.

Dr. Cattell: I think this aspect of the action of BAL is an important one because, at least in the experimental animal, although the animal may be saved, the amount of arsenic excreted may represent a very small fraction of the dose of the metal which was given.

Dr. Riker, would you tell us of the interesting experiments which you carried out with Dr. Rosenfeld showing the shift of arsenic from the cells?

Dr. Riker: We found that the arsenic content of the blood plasma increased after BAL was administered to an animal poisoned with arsenic, and that this was associated with a release of arsenic by the cells.

Dr. Cattell: It disappears from the red blood cells and apparently accumulates in certain tissues, particularly in the reticulo-endothelial system, suggesting that there may be storage there.

Dr. Chenoweth: In connection with the use of BAL for the treatment of toxic effects of the arsenicals in the therapy of syphilis, it might be well to mention that the BAL not only protects the patient's tissues against the arsenic, but also protects the spirochete against the arsenic. The result is that the antisyphilitic therapy is no longer effective if BAL is used at the same time.

Dr Kensler Does BAL block the action of the mercurial diuretics?

Dr Cattell There are now several studies which show that BAL reduces the toxicity of the mercurial diuretics

Visitor One paper, as I recall referred to this antagonism in the case of the cardiotoxic effects of the mercurial diuretics Is there any information as to the effect of BAL on the diuresis produced by the mercurials?

Dr Cattell There is evidence that it does that, too If the BAL mercurial complex produced diuresis, it might be a great advantage

Dr Riker On the basis of our information one would expect BAL to antagonize all actions of the mercurial diuretic I would expect it to check the diuretic effect of the mercurials by preventing the interaction of the mercury with the protein of renal tubules

Mr Donald A Clarke There is unpublished work indicating that BAL not only inhibits the diuresis of the mercurial but, in addition has an antidiuretic action of its own

Dr Cattell The effect of BAL on the excretion of metals seems to me one of the most impressive aspects of the action of this compound Perhaps Dr Riker would describe the typical course of arsenic excretion after a dose of BAL.

Dr Riker After a single test dose of BAL in a case of arsenic poisoning there is usually a sharp rise in the urinary excretion of arsenic in the next 24 hour specimen This is followed by a rapid return to the control level Such was the case, for example in the patient with arsenical jaundice to whom I have already referred Before the BAL was started, the concentration of arsenic in the urine was rather low considering the amount of arsenic that had been given The administration of several doses of BAL in this case produced a very sharp increase in the urinary arsenic, on the following day, the concentration was about 4 times that of the control On the day after, however, the concentration had returned to the control

level in spite of the fact that the administration of BAL was continued The high icteric index and the symptoms of poisoning showed a rapid reversal A point of importance here is the possibility that the BAL may continue to exert a beneficial effect even during the period when the level of arsenic excretion in the urine is not substantially elevated It would seem reasonable therefore to continue the use of BAL in the presence of clinical evidence of arsenical poisoning even when the arsenic excretion level in the urine is not elevated but one should bear in mind that the complete healing of arsenical lesions even after the arsenic is removed may take a fairly long time The decision as to how long the BAL therapy should be continued will require a great deal more clinical experience The difficulty of determining how long BAL treatment should be continued is well illustrated by the problem of arsenical hepatitis There has been some debate among syphilologists concerning the exact nature of the jaundice complicating arsenotherapy There is reason for believing that if it responds promptly to BAL therapy the jaundice is clearly due to the arsenic directly although there still remains the possibility that a delay in response or even a failure in response may be due to the persistence of a liver damage produced by arsenic or by some complicating factor

Student Is BAL equally effective against arsenic taken in a variety of forms such as Paris green and rat poisons?

Dr Cattell It is in experimental animals The one known exception arsine which Dr Kensler mentioned is at present, of no practical importance

Dr Riker It is effective against Fowler s solution which is an inorganic arsenic preparation Dr Walsh McDermott and I treated a very severe dermatitis resulting from Fowler s solution The dermatitis was similar to a bullous pemphigus with large bullae over the entire body The patient was seriously ill at the time of admission as the result of secondary infection and fluid loss from the rupture of the bullae Previous non

specific therapy had been of no avail The history revealed that the patient had been given Fowler's solution for a minor skin condition a number of years before, and that he continued the medication on his own by drinking from the bottle daily without concern We started BAL therapy, and the response was dramatic. Prior to BAL there was a very low level of arsenic excretion, whereas following it there was a tremendous outpouring of arsenic in the urine, and the lesions started to clear Sulfadiazine therapy was instituted to control the secondary infection The patient was well in about 3 weeks except for peripheral neuritis which cleared up a few months after discharge Other cases of poisoning by Fowler's solution have been reported, which responded well to BAL therapy

SUMMARY

Dr Gold We may now summarize the essential points covered in the conference this afternoon The history of specific antidotes to poisoning by metals is substantially an account of unfulfilled promises Sodium thiosulfate was introduced in 1920 as an antidote to arsenic poisoning Its use was continued for many years, although proof of its value was never very impressive It was applied to bichloride of mercury poisoning but, again, it was not long before it became fairly clear that its value was negligible You may recall the episode having to do with sodium formaldehyde sulfoxalate as an antidote to bichloride of mercury poisoning It began in 1934 and even though some have continued to use it up to the present time the indication is fairly clear that the antidote has to be given before the poison in order to provide a conspicuous protective action in systemic poisoning with bichloride of mercury

The long succession of failures of suggested antidotes to metal poisoning was interrupted in the early days of World War II by a series of important discoveries made in rapid succession in the co-operative war programs of chemical pharmacologic, and clinical research, focused on the problem of

an antidote to the arsenical vesicant lewisite The chief practical issue was the synthesis of the compound BAL which is not only highly effective in preventing tissue damage by arsenic and mercury but in reversing moderate grades of tissue injury after the metals have been at work for some time

Some of the numerous lines of investigation leading to this discovery were reviewed this afternoon Many important steps were necessary before the problem arrived at the point at which an effective antidote became available One of the earliest observations bearing most directly on the subject was that of Voegtlin Dyer, and Leonard of the United States Public Health Service who in 1923 advanced the view that the therapeutic arsenicals produce their effects by combining with the -SH groups of protoplasm There were the observations that various enzyme systems depended for their activity on free -SH groups that these enzyme systems could be poisoned by arsenicals that the combination in some types of thioarsenites could be reversed in alkaline solution that monothiol and some dithiol compounds with arsenic were as toxic as the arsenical itself observations leading to the belief that fairly stable but reversible ring compounds might be formed between the arsenical and the SH groups of tissue proteins or the *protein portion of the enzyme systems* that *similar* but less easily dissociable compounds of the arsenicals are formed by their interaction with simple dithiols which can compete successfully with the tissue dithiols for the toxic metal

The compound 2 3-dimercaptopropanol more popularly known as British anti lewisite or BAL, is not a harmless material It is itself a poison It is irritant to the skin and mucous membranes and in large doses causes death with capillary paralysis and shock *sometimes preceded by* convulsions It causes lacrimation blepharospasm salivation vomiting muscular cramps unrest apprehension and weakness Small doses produce arteriolar constriction with elevation of the blood pressure It is noteworthy that unpleasant effects are produced

specific therapy had been of no avail The history revealed that the patient had been given Fowler's solution for a minor skin condition a number of years before, and that he continued the medication on his own by drinking from the bottle daily without concern We started BAL therapy, and the response was dramatic. Prior to BAL there was a very low level of arsenic excretion, whereas following it, there was a tremendous outpouring of arsenic in the urine, and the lesions started to clear Sulfadiazine therapy was instituted to control the secondary infection The patient was well in about 3 weeks except for peripheral neuritis which cleared up a few months after discharge Other cases of poisoning by Fowler s solution have been reported, which responded well to BAL therapy

SUMMARY

*Dr Gold We may now summarize the essential points cov*ered in the conference this afternoon The history of specific antidotes to poisoning by metals is substantially an account of unfulfilled promises Sodium thiosulfate was introduced in 1920 as an antidote to arsenic poisoning Its use was continued for many years, although proof of its value was never very impressive It was applied to bichloride of mercury poisoning but, again, it was not long before it became fairly clear that its value was negligible You may recall the episode having to do with sodium formaldehyde sulfoxalate as an antidote to bichloride of mercury poisoning It began in 1934 and even though some have continued to use it up to the present time the indication is fairly clear that the antidote has to be given before the poison in order to provide a conspicuous protective action in systemic poisoning with bichloride of mercury

The long succession of failures of suggested antidotes to metal poisoning was interrupted in the early days of World War II by a series of important discoveries made in rapid succession in the co-operative war programs of chemical pharmacologic, and clinical research, focused on the problem of

an antidote to the arsenical vesicant lewisite The chief practical issue was the synthesis of the compound BAL which is not only highly effective in preventing tissue damage by arsenic and mercury but in reversing moderate grades of tissue injury after the metals have been at work for some time

Some of the numerous lines of investigation leading to this discovery were reviewed this afternoon Many important steps were necessary before the problem arrived at the point at which an effective antidote became available One of the earliest observations bearing most directly on the subject was that of Voegtlin Dyer, and Leonard of the United States Public Health Service who in 1923 advanced the view that the therapeutic arsenicals produce their effects by combining with the -SH groups of protoplasm There were the observations that various enzyme systems depended for their activity on free -SH groups that these enzyme systems could be poisoned by arsenicals that the combination in some types of thioarsenites could be reversed in alkaline solution that monothiol and some dithiol compounds with arsenic were as toxic as the arsenical itself observations leading to the belief that fairly stable but reversible ring compounds might be formed between the arsenical and the SH groups of tissue proteins or the protein portion of the enzyme systems that similar but less easily dissociable compounds of the arsenicals are formed by their interaction with simple dithiols which can compete successfully with the tissue dithiols for the toxic metal

The compound 2 3-dimercaptopropanol more popularly known as British anti lewisite or BAL, is not a harmless material It is itself a poison It is irritant to the skin and mucous membranes and in large doses causes death with capillary paralysis and shock sometimes preceded by convulsions It causes lacrimation blepharospasm salivation vomiting muscular cramps unrest apprehension and weakness Small doses produce arteriolar constriction with elevation of the blood pressure It is noteworthy that unpleasant effects are produced

Treatment of Hepatic Insufficiency

Dr. Paul A. Bunn: The conference on the treatment of hepatic insufficiency will be opened by Dr. Daniel H. Labby of the Rockefeller Institute. Work on this problem, now in progress at the Institute, has borne results in the form of important therapeutic measures as well as of advances in understanding of the complex physiology of the liver.

Dr. Daniel H. Labby: Knowledge in the field of liver physiology has been won laboriously, because liver functions are not only multiple, but are often performed in co-operation with other organ systems also ill-understood. Since rational therapy must be directed at the physiologic mechanisms involved, progress in the therapy of liver disease has awaited advances in many fields. Because of the progress in biochemistry, nutrition, and metabolism, and the large experience in clinical liver disease during World War II, great strides are being made in establishing the therapy of liver disease on a more secure basis than that of the past. We have time today to consider the problems arising from two forms of hepatic insufficiency, acute infectious hepatitis and cirrhosis. The first is an example of aberrant liver function resulting from a relatively rapid and diffuse insult to the liver. Here a severe degree of hepatic insufficiency may develop quickly. The second, cirrhosis, is an example of insidious, progressive insult to the liver, the clinical manifestations of which may not appear until late in the disease.

Acute hepatitis has been considered to be a self-limited dis-

ease In over 375 cases studied at the Rockefeller Institute Hospital there have been no deaths, although the general mortality of the disease is approximately 0 3 per cent Therapy depends on early recognition, followed by bed rest and regulation of nutrition during the acute phase, and the careful supervision of activity in convalescence

The value of bed rest in the acute phase may be examined first An outbreak of hepatitis occurred in the U S Army in 1942, resulting from the accidental inoculation of over 100,000 soldiers with an icterogenic lot of yellow fever vaccine It was observed that often the disease developed soon after a period of exposure to inclement weather or prolonged physical strain Convalescence was frequently retarded in those individuals hospitalized late in the course of their disease, and recrudescences appeared in those patients discharged after relatively short periods of hospitalization Vigorous exercise too soon after discharge from the hospital had a similar effect It was a matter of grave concern in the armed services to note the rising number of hepatitis casualties developing in active war theaters Many of these cases required repeated hospitalizations because they were returned to duty too early in convalescence It was therefore, a matter of some military importance to determine the minimal hospitalization period, as well as the criteria for a 'cure' An analysis was made of the effects of hospitalization, rest, and activity on the clinical course of 200 Naval cases at the Rockefeller Institute Hospital Many of the patients had arrived promptly after onset of their disease, others had been delayed en route because they had become ill while at sea, or had presented some diagnostic difficulty at first It was possible, therefore, to examine the overall effect of these varying circumstances on the duration of convalescence and the severity of the clinical course in the average case of hepatitis

The Naval personnel with acute infectious hepatitis, admitted to the Rockefeller Institute Hospital, were divided into

phosphorus, and carbon tetrachloride injury The important rôle of nutritional factors in liver disease was further indicated by the discovery in 1924 that a depancreatized dog would die with a fatty liver even if insulin were administered, but that groundup pancreatic tissue added to the diet would prevent death Nine years later, in 1933, Rao, working in southern India, discovered cirrhosis in a nonalcoholic group of natives living on a diet of rice, who also displayed other nutritional deficiencies Gilbert and Gillman reported a high incidence of cirrhosis in South African natives in whom other dietary deficiency diseases were common, and who subsisted on meager amounts of corn (maize), occasionally supplemented by fermented cow s milk Rats fed the same diet also developed cirrhosis There is, however, some disagreement among pathologists concerning the similarity of this cirrhosis to human cirrhosis By 1939, when Goldschmidt and Whipple demonstrated the protective action of protein, the focus on the rôle of nutrition sharpened Sebrell produced cirrhosis in rats with diets low in casein and choline, and then demonstrated that this was a reversible phenomenon when casein and choline were added to the diet Extensive regeneration and hyperplasia of the liver accompanied this reversal

It is this type of data that suggests the value of the high protein diet The value of supplemental choline awaits more extensive clinical trial A study recently reported by A J Beams, of Western Reserve University, presents pertinent data Twenty two cases of cirrhosis with ascites received a high protein diet alone and a similar number, a high protein diet plus supplemental choline and cystine At the end of 1 year, 12 of the cases treated with choline and cystine had improved to the extent of losing ascites, the remaining 10 had died Of the untreated group, only 6 were still alive It is of interest that all of the improved cases had enlarged livers which may indicate that they were early cases No comment is made as to the exact dietary intake in the untreated cases

The rationale of a low fat diet in cirrhosis may also be argued from these facts since choline and methionine are lipotropic However, there is little convincing evidence that the diets containing moderate amounts of fat are harmful in cirrhosis Indeed, an analysis of several so called low fat diets indicates that much of the protein included is lipid bound, and when metabolized affords a source of fat not usually calculated in the diet In planning diets therefore, dieticians should consider lipoproteins as potential sources of fat The advantages of fat in enhancing palatability and affording better supplies of fat soluble vitamins and certain essential unsaturated fatty acids has been mentioned During the episodes of acute hepatic decompensation that punctuate the clinical course of cirrhosis, when high degrees of biliary obstruction are present, digestive upsets may be avoided by a temporary reduction in fat intake

Emphasis has been placed on the nutritional factor in cirrhosis by Patek and his coworkers who observed the frequent clinical coincidence of beriberi and pellagra like syndromes in alcoholics and the occurrence of alcoholism in cirrhotic patients They suggested there might be a correlation between alcoholism and cirrhosis on the basis of coexisting nutritional deficiencies They treated a group of cirrhotic patients with a highly nutritious high protein diet supplemented with large amounts of vitamin B complex and brewer s yeast Of an untreated control group 22 per cent were alive at the end of 2 years 45 per cent of the treated group were alive at the end of this time Experimentally it is difficult to obtain water tight evidence that vitamins of the B group protect the liver from injury or that the metabolism of this group of vitamins is faulty during hepatic insufficiency

In the case of vitamin A however, evidence is more pointed Not only is 95 per cent of vitamin A stored in the liver, but this organ is the only important site of the conversion of carotene and the carotenoid pigments into vitamin A. The vitamin

A content of the cirrhotic liver may be as low as 10 per cent of normal, and at least 50 per cent of cirrhotic patients have defective dark adaptation and night blindness (nyctalopia) There is, therefore reason to provide an adequate intake of vitamin A source foods and to insure that plenty of carotenes are available for conversion to vitamin A within the capacity of the liver to do so

An occasional case with osteomalacia and osteoporosis suggests the need for vitamin D Bile salts and additional calcium might be utilized to insure adequate intestinal absorption With high protein diets however, the calcium intake is materially enhanced A depression in vitamin K activity is common in long standing cirrhosis and is indicated by low prothrombin values Too often one encounters prothrombin levels that are fixed at moderately low levels and are rigidly unresponsive to vitamin K Clinical experience suggests that fairly good residual liver function must remain to permit an effective response

The use of blood and blood products has received much attention in nutritional problems during the war Worthy of attention are the studies of Thorn on salt poor human albumin solutions as intravenous adjuvants in patients having low serum albumin levels He treated 5 cirrhotic patients for from 1 to 10 days with 50 Gm of albumin administered intravenously daily while maintaining them on adequate diets low in salt Those patients treated for from 1 to 3 days developed a diuresis and mobilized their edema with a resulting weight loss In the absence of edema diuresis was not observed with short periods of treatment despite the presence of ascites Conspicuous elevation of the serum albumin was produced proportional to the amount of albumin administered Little of this albumin appeared in the urine and 50 to 80 per cent was retained as measured by nitrogen balance studies Thorn suggests this as a promising form of therapy in (1) the severe cirrhotic patient who on dietary treatment alone can be main

tained in positive nitrogen balance but who cannot elevate his serum albumin and (2) long standing acute hepatitis when anorexia gravely compromises dietary intake discouraging positive nitrogen balance and normal blood albumin levels

We have had occasion to use this form of therapy in 6 cases of cirrhosis with ascites In all but 2 far advanced cases there was an impressive diuresis followed by disappearance of the ascites One patient after one course of therapy has been free of ascites for 3 months Another has been kept free of ascites with occasional re treatment and without additional treat ment has recently enjoyed 2 months without ascites A third case required weekly abdominal paracentesis prior to albumin therapy but has since begun to void freely and spontaneously and has had no further edema or ascites for 1 month A fourth case now under treatment required paracentesis every 2 weeks for a period of 5 months prior to therapy A dose of 100 Gm of albumin given daily for 4 days has produced an im mediate diuresis with absorption of the ascites and edema The fifth and sixth cases are far advanced but have shown some diminution in ascites and edema with an accompanying diure sis Although their improvement has been less dramatic than that of the first four they have shown a visible increase in body tissue and decreased tendency for tissue wasting More data are necessary for a final evaluation of this form of therapy

The value of a crude water soluble extract of Cohn s liver fraction G from which pyrogens have been extracted is under scrutiny now at the Rockefeller Institute Hospital and New York University Medical Service of Bellevue Hospital One may safely give 10 to 20 cc of this extract diluted to 50 cc with normal saline 2 to 3 times per week if preliminary tests of tolerance and sensitivity are worked out first Statistics are now being compiled on 2 year experience with a group of patients who have been allowed to eat a diet much of their own choice but in addition have received 20 cc. of liver extract intrave nously 2 to 3 times weekly

While we have the impression that results have been (couraging, final conclusions await the completion of our ana sis. However, three sets of data are available for a rough co parison of treatment regimens in cirrhosis of the liver. T work of Patek and his group has shown that in an untreat control group of 386 cases taken from hospital records, only per cent survived the first 2 years after the onset of some for of hepatic decompensation such as ascites, edema, icterus, hematemesis. In a treated group of 54 similar patients, close observed while on a highly nutritious diet with large supp ments of vitamin B and brewer's yeast, 45 per cent surviv the 2-year period.

The New York University group, employing a crude i travenous liver extract, reports that at the end of 2 years, ir group of 33 cases of cirrhosis with ascites, treated by diet ar moderate vitamin B supplementation, but not brewer's yea 25 per cent survived. In 27 similar cases receiving the san dietary management plus crude intravenous liver extract, (per cent survived the 2-year period. The group studied at tl Rockefeller Hospital has been a bit more fortunate. It w composed of 33 cases of cirrhosis, representing all forms (hepatic decompensation, treated with liver extract and o served over a 2-year period. Of this group, 28 patients, or 8 per cent, have survived to the present time. It should be ir dicated, however, that these patients represent a more fort nate economic group, and are probably more co-operativ They have shown remarkable loyalty to biweekly therapy, an with few exceptions, have discontinued drinking alcohol. Or cannot overemphasize the significance of these difference since the more difficult and less co-operative patients studie by Patek and the New York University group probably ir clude severely addicted and chronically malnourished alc holics. In addition, it should not be forgotten that our patient were able to exercise wide selection in their diet, so that ir most cases it included a high-caloric and well-balanced die

with adequate complements of animal and dairy proteins and natural sources of vitamins A more detailed analysis of our data is being undertaken at the present time

The patient with cirrhosis has many requirements Most of these may be met by a high protein, high carbohydrate, moderate fat diet, supplemented with vitamins A, K, and, perhaps, D, the value of choline remains controversial and awaits greater experience On the basis of the available evidence it is reasonable to assume that cirrhosis is a multiple deficiency state, of which we recognize only a few specific deficiencies which we can relieve It is reasonable, therefore to consider a diverse type of adjuvant therapy for such a complex syndrome involving so many as yet unrecognized metabolic defects It is possible, in this manner, that with crude liver extract we may supply necessary factors not yet implicated

Dr S S Lichtman The question of bed rest is one which I think needs no further emphasis here One should insist on bed rest even in the mildest cases of infectious jaundice In the past these have been considered too often as unimportant ill nesses

A negative nitrogen balance exists in liver disease However, we must place these patients in a different category from those immobilized because of fractures in whom the immobilization appears to cause the negative nitrogen balance although this factor may also operate in liver disease Large amounts of protein are also needed for regeneration This would not change the plan of treatment since the requirements of the ailing liver include huge amounts of protein Often because of poor food intake prior to the onset of his illness the patient has already depleted his protein stores

Every case of simple hepatitis or old fashioned catarrhal jaundice is a candidate for liver atrophy I think it is most important to have the patient under observation not only to feed him well, but also to observe every change from day to day When the patient is under constant supervision the physician

is more likely to detect that point at which the disease process may advance into a serious stage of chronic liver disease and act accordingly

As far as the factors of nutrition and diet are concerned, I find that *the tendency now is for the younger physicians to think more about the new and forget the old* Some of the concepts which we have held for years had their origin in sound laboratory work One of the older, *sound measures is the high* carbohydrate diet supplemented with intravenous glucose infusions Pathologists are now finding only rarely the type of liver encountered more commonly three and four decades ago when patients did not receive the high-carbohydrate diet Therapy is apparently modifying the pathologic picture Patients are now taking methionine and choline religiously but *unless the whole of the dietary intake is also zealously super*vised treatment is incomplete Whether or not choline proves to be of permanent value in the treatment of liver disease I am impressed with its effect on the appetite Choline may bring about improved appetite directly or indirectly It may correct vitamin B deficiency, or influence gastric motility through an acetylcholine mechanism Whatever the mechanism is the patient receiving choline is better able to cooperate with the enforced feeding program because anorexia is *less marked Thus although given for its lipotropic activity* choline may prove to be of therapeutic value in a different manner

Recently a paper by Barker Capps and Allen appeared in the *Journal of the American Medical Association*, describing a new syndrome in which patients with hepatitis suffered a relapse when they were permitted to leave their beds and engage in activities prematurely *This publication* rendered a great service not so much in the development of the theme of a so-called new clinical syndrome but more in vividly emphasizing the need for continued bed rest in hepatitis despite the fact that the clinical impression is one of arrest of the disease It is

wise to continue bed rest from 4 to 6 weeks after liver function tests return to normal or become stabilized The patient is at first permitted bathroom privileges and sitting at the bedside The first venture outdoors is attempted from 4 to 6 weeks later provided liver function tests remain stabilized

I would like to comment on the currently improved results in patients with ascites The first set of data presented indicated that control cases treated with intravenous saline infusions fared as well as the experimental group receiving choline and methionine The deduction seems obvious yet another interpretation is admissible In addition to intravenous saline the control group was receiving the optimum basic regimen high protein high-carbohydrate diet etc The therapeutic value of choline and methionine per se in the experimental group may be lost in a statistical survey of this type of material A more satisfactory evaluation of these agents might be made in a group of patients with cirrhosis of long standing with innumerable paracenteses and marked protein depletion The studies to date are of limited value in ascertaining the specific value of choline methionine or liver extracts in obtaining the improved clinical results. The value of bed rest vitamin K therapy and ample diet must also be reckoned with There is a definite advantage in any method which reduces the number of paracenteses required in the reduction of protein loss as well as in reduction of the risk of peritoneal infection

I would like to inquire about the cases receiving the salt poor albumin How much albumin was given to bring about the impressive results? Was the quantity of albumin insignificant compared to the remarkable diuresis established or was the albumin given in such quantities as to change the plasma protein pattern and protein reserves in the tissues?

Dr Bunn Dr Labby would you care to comment?

Dr Labby As I have indicated we have treated only 6 cases The procedure was as follows In the morning patients were given 25 Gm of albumin dissolved in 100 cc which is ad

ministered rather rapidly. They can be given an additional 25 Gm. in the afternoon so that the total intake for the day would be 50 Gm. of albumin. We discovered later that as much as 200 Gm. of albumin could be given in one day with perfect safety. In one case, the initial plasma albumin was about 1.9 Gm. per cent. Following 2 days of 200 Gm. of albumin daily, the plasma albumin rose to approximately 2.8 Gm. per cent. Is that correct, Dr. Shank?

Dr. Robert E. Shank: It finally reached 4 Gm.

Dr. Labby: After how much total therapy?

Dr. Shank: After 500 Gm. of albumin.

Dr. Sidney Greenberg: One of the remarkable effects following the use of albumin, in some cases, is the immediate tendency toward reversal of the albumin-globulin ratio, as though the patient were better able to utilize globulin. In such cases the globulin level may drop while the total protein remains the same. Do you find that to be true?

Dr. Labby: Yes, with supplements of albumin, because the total plasma albumin can be so materially enhanced, the total protein may even rise despite falling globulin values. There is also an increase in plasma volume so that at least part of the effect on the globulin is due to dilution.

Dr. Greenberg: I would like to ask two questions. How much salt is in your diet? In these patients with cirrhosis of the liver, was it thought that the ascites developed because of increased portal pressure?

Dr. Charles L. Hoagland * *:* We know that in some cases of cirrhosis there is portal hypertension and that can account for the fluid. However, the experiments performed on the surgical service of Presbyterian Hospital indicate that the portal pressures as measured from the splenic vein do not always correlate. Consequently, the tendency to ascites may have more to it than that.

Dr. Labby: About the salt, Dr. Greenberg, at the present

* Dr. Hoagland died August 2, 1946.

time we have patients on what we call a low salt diet The food is cooked with salt, but the patient gets none on the tray As a substitute, a salting agent which does not contain sodium chloride is used

Dr Greenberg Would you comment on the use of the mercurial diuretics in patients with edema due to cirrhosis?

Dr Labby I can give my own impression It may work temporarily but it does not strike at the basis of the mechanism of edema formation, the hypoproteinemia It is certainly the uncommon case of hepatic decompensation which is appreciably benefited by mercurial diuretics

Dr Hoagland Often they are completely ineffective

Dr Labby Yes most cases appear to be relatively refractory to mercurial diuretics

Dr Walter Modell I have just reread the conference on mercurial diuretics in the first published volume of these conferences, in which considerable discussion fails to arrive at an explanation for the difference between the action of the mercurial diuretics in cardiac ascites and cirrhotic ascites Perhaps you can give us the answer Why is it that usually there is a dramatic result in cardiac failure and so frequently none at all in the case of the ascites and edema of cirrhosis?

Dr Labby If the mercurial diuretics act in part by increasing salt excretion one would expect a greater effect in cardiac failure with ascites than in cirrhosis with its associated hypoproteinemia

Dr Hoagland Some of us believe that there may be a hormonal influence which contributes to the picture of cirrhotic ascites It is becoming increasingly evident that there are large amounts of estrogenic substances which appear in the urine Certainly, the estrogenic substances can modify water balance, as we know in the premenstrual and similar states, where the estrogenic output may reach great heights In the male the 17 ketosteroids which indicate the course of androgenic metabolism are greatly diminished in the urine We know, more-

over, that in most cases with ascites, there is a phenomenal increase in antidiuretic substances in the urine. I think all these things have to be taken into account for the final explanation of the phenomenon of ascites. Certainly these factors are of less importance in the ascites of nephrosis and of cardiac failure.

Visitor: Dr. Lichtman mentioned the importance of the early detection of unfavorable signs in liver disease. I would like to know what the signs are and what can be done when they are detected.

Dr. Lichtman: Patients who are under active treatment, whether jaundiced or not, and who show signs of liver damage, must have a battery of liver function tests performed at least at weekly intervals, to observe the various aspects of the course of the disease. These indicate whether the patient is improving or not, even though the degree of visible jaundice appears unchanged. The tests include the albumin-globulin ratio. A rise in albumin and/or total protein is a very favorable sign. A normal albuminemia which drops, say 50 per cent, in spite of therapy, would be an ominous sign. The cholesterol ester fraction is also significant. A decline in the total cholesterol and the ester fraction simultaneously indicates progressive liver damage. The galactose tolerance test often helps to differentiate liver damage from biliary obstruction. When routine facilities are not available for the estimation of amino acids in the blood, the urea–nonprotein nitrogen ratio is most helpful in advanced hepatic failure. A rise in the blood nonprotein nitrogen and a fall in the blood urea are found under these circumstances. Additional routine tests performed are the icterus index, the bromsulfalein test, the cephalin-cholesterol flocculation, and thymol turbidity reactions. Guided by the results of these tests, the attending physician is in a better position to determine the severity of the illness and treat the patient more intelligently.

Dr. Thomas P. Almy: The use of parenteral amino acids has been suggested when the oral intake is not adequate in acute

hepatitis. I wonder if we need fear the failure of deamination of these substances in the liver.

Dr. Hoagland: I can cite some experimental work. We have studied not only the ammonia nitrogen but the total nitrogen. The excretion of homologous keto acid appearing after various amino acids provides important information. These can now be measured with considerable ease. We have not encountered much difficulty on the part of the decompensated liver to deaminate amino acids. This is evident from the extraordinary amounts of keto-acid and keto derivatives excreted, which show that the deaminating mechanism is intact although the metabolism of amino acids is incomplete. Only in very advanced states of hepatic insufficiency is there failure to deaminate. In none of our cases of hepatitis, and over 100 were studied with that in mind, was there any evidence of impaired deamination in so far as it was reflected in ammonia excretion and in the excretion of homologous acids of keto hydrates.

Dr. Labby: I think it might be mentioned in that respect too, Dr. Hoagland, that a patient may die from liver insufficiency with a normal blood urea nitrogen.

Dr. Hoagland: That happens very frequently.

Dr. Bunn: I would like to ask one question. You suggested all patients with acute hepatitis should refrain from alcohol. Is that restriction permanent?

Dr. Labby: We happen to be working with a group of men who are in the Navy, and we appreciate, therefore, that we have two strikes against us. The usual warning to the patient about alcohol is certainly not to drink at all during the 10-day leave period that follows convalescence. The patient on final discharge from the hospital is warned that at least a 6-months' period should elapse before hard liquor is taken. They always ask, "How about an occasional beer?" Since one beer usually leads to another, complete restriction is probably advisable. How completely they will accept this is an individual matter.

The restriction, however, extends at least 6 months in a case which has gone on to measurable damage.

Dr. Almy: As I recall, Dr. Hoagland suggested that some of these cases of hepatitis go on to actual cirrhosis. What proportion of patients with cirrhosis have developed it because of a preceding hepatitis?

Dr. Hoagland: In our series, at least, that is undecided at the moment, because the patients have not been observed for a long enough period. Some of these cases have been discharged with all the criteria of recovery, but some of them may develop cirrhosis eventually.

Dr. Lichtman: We have some information on that in Dr. Patek's monograph on the records of over 400 cases in the files of several large hospitals in New York City. Of the patients with portal cirrhosis, 6 per cent istory of previous attacks of jaundice. On this basi sumed that the cir rhosis was a posthepatitic comp

Dr. Hoagland: If hepatitis w tant cause of ci rhosis we should expect to see m an we do amo the numerous cases of hepatitis.

Dr. Labby: The figures for th epatitis va in the literature, from 3 to as muc We are o now recognizing cases of acute i 's with jaundice; they may have liver en der and the entire syndrome, but may tient with cirrhosis, therefore, may diagnosis never suspected because of

SUMMARY

Dr. Harry Gold: The conference th the treatment of hepatic insufficiency, infectious hepatitis and hepatic cirrho

Infectious hepatitis is a common d million people in the United States. It is the rule after a protracted period o

tion has been made that some of these cases may be the precursors of hepatic cirrhosis although it seems to be clear that most cases of hepatic cirrhosis represent an independent disease which runs an insidious course and usually comes under treatment in the advanced stage in which the disability is largely the result of hepatic insufficiency

The specific therapeutic needs in any particular case of infectious hepatitis for the most part are inferred from metabolic studies the nature of the disturbances in blood chemistry, and from the results of a variety of liver function tests which may show such disorders as an abnormal nitrogen balance low blood proteins with disturbance in the normal blood protein pattern diminished prothrombin and diminished storage and utilization of various vitamins The same tests provide useful guides to the course of recovery While it does not necessarily follow that abnormalities such as low blood proteins or low blood prothrombin or the like can be corrected by the administration of the corresponding agents experience has shown that the feeding or the parenteral administration of those materials which are quantitatively subnormal in hepatic insufficiency has a beneficial influence on the course of the disease

Opinion appears to be unanimous that bed rest is of paramount importance in the recovery from infectious hepatitis The disease shows a very limited tendency to subside while the patient is up and about it lasts on the average about a month if the patient is put to bed shortly after the onset but if the patient is up and about for a period of let us say a month after the onset he may still require a period of about a month of bed rest to insure recovery

The literature contains reports of special benefits derived from various specialized diets In the conference today we have heard from those with a large experience in the treatment of these cases that no special diet does any better than one that is well balanced and high in calories This one was suggested

as optimal: 400 Gm. of carbohydrate, 125 Gm. of protein, and from 80 to 90 Gm. of fat. The fat not only adds to the calories but makes the food more palatable. This helps to solve the problem of an adequate caloric intake, since these patients suffer with anorexia and their nutritional state is apt to deteriorate unless an intake of sufficient calories can be insured. If there is appreciable lowering of the blood prothrombin level, vitamin K by parenteral administration is added. If the blood proteins are significantly lowered, parenteral preparations are tried, such as protein hydrolysate, whole blood, human plasma, or albumin. Specific measures directed in part toward reversing the process in the liver itself, such as choline, methionine, and the Cohn fraction G of liver have been tried, but there is as yet no satisfactory proof that they alter the course of the disease.

In the management of hepatic cirrhosis, essentially the same principles are utilized. A diet similar to the one prescribed for infectious hepatitis may be used. Since the disease is one of long duration, depletion of vitamin stores may become a matter of considerable importance, especially vitamin A which is stored largely in the liver. Vitamin D and K may be absorbed poorly. Large doses of all of these are often desirable. There is some indication that the Cohn fraction G of liver may prove to be useful. The edema and ascites due to hepatic cirrhosis are somewhat resistant to treatment. The mercurial diuretics are of some value. The salt-poor albumin introduced by Thorn has proved useful in some cases for the control of the disturbance in water metabolism of the cirrhotic patient.

In hepatic insufficiency, fried fats should be withheld, and alcohol, because of its damaging action upon the liver, is contraindicated. In the use of such medications as morphine and the barbiturates, attention needs to be paid to the matter of doses and intervals between them, since these agents depend largely on liver function for their elimination.

Patients with hepatic insufficiency are poor surgical risks, a

factor which requires special attention in relation to elective surgery.

As matters stand in the treatment of infectious hepatitis and hepatic cirrhosis, measures are directed chiefly toward the maintenance of general nutrition. Although observations in animals provide interesting possibilities, there are as yet no specific agents which are known to reverse the abnormal process in the human liver. However, it may well be that the maintenance of a satisfactory metabolic balance may protect the liver and help to restore its structure and function. The fact remains that with such measures as have been outlined in the conference today patients with infectious hepatitis recover more quickly, and patients with hepatic cirrhosis live longer.

as optimal: 400 Gm. of carbohydrate, 125 Gm. of protein, and from 80 to 90 Gm. of fat. The fat not only adds to the calories but makes the food more palatable. This helps to solve the problem of an adequate caloric intake, since these patients suffer with anorexia and their nutritional state is apt to deteriorate unless an intake of sufficient calories can be insured. If there is appreciable lowering of the blood prothrombin level, vitamin K by parenteral administration is added. If the blood proteins are significantly lowered, parenteral preparations are tried, such as protein hydrolysate, whole blood, human plasma, or albumin. Specific measures directed in part toward reversing the process in the liver itself, such as choline, methionine, and the Cohn fraction G of liver have been tried, but there is as yet no satisfactory proof that they alter the course of the disease.

In the management of hepatic cirrhosis, essentially the same principles are utilized. A diet similar to the one prescribed for infectious hepatitis may be used. Since the disease is one of long duration, depletion of vitamin stores may become a matter of considerable importance, especially vitamin A which is stored largely in the liver. Vitamin D and K may be absorbed poorly. Large doses of all of these are often desirable. There is some indication that the Cohn fraction G of liver may prove to be useful. The edema and ascites due to hepatic cirrhosis are somewhat resistant to treatment. The mercurial diuretics are of some value. The salt-poor albumin introduced by Thorn has proved useful in some cases for the control of the disturbance in water metabolism of the cirrhotic patient.

In hepatic insufficiency, fried fats should be withheld, and alcohol, because of its damaging action upon the liver, is contraindicated. In the use of such medications as morphine and the barbiturates, attention needs to be paid to the matter of doses and intervals between them, since these agents depend largely on liver function for their elimination.

Patients with hepatic insufficiency are poor surgical risks, a

factor which requires special attention in relation to elective surgery

As matters stand in the treatment of infectious hepatitis and hepatic cirrhosis measures are directed chiefly toward the maintenance of general nutrition Although observations in animals provide interesting possibilities there are as yet no specific agents which are known to reverse the abnormal process in the human liver However it may well be that the maintenance of a satisfactory metabolic balance may protect the liver and help to restore its structure and function The fact remains that with such measures as have been outlined in the conference today patients with infectious hepatitis recover more quickly and patients with hepatic cirrhosis live longer

Management of Pain Due to Muscle Spasm

Dr Harry Gold The conference *today is on the subject of* the relief of pain which arises in association with the contraction of muscle *In* some respects the problems here are similar to those of pain arising in other structures Central analgesic agents such as morphine, codeine demerol and salicylates relieve pain in muscles as they do other forms of pain Muscle pain however also presents some special problems in therapy Drugs are used *in the case of muscle pain not only to reduce* perception of pain in the brain centers but to attempt to relax the muscle presumably for the purpose of eliminating the source of the painful impulse The term muscle spasm is often applied in relation to these problems and the drugs employed for the relief of such painful states are classified as antispasmodic agents

The conditions are numerous namely the pain of coronary artery disease peptic ulcer, spastic colon biliary colic renal colic *intermittent claudication menstrual pain labor pain* and pain in various disorders of the skeletal muscles

*I am not sure that we are altogether clear on what is happen*ing in the so called spastic muscle which gives rise to pain and how we expect the drugs to act in order to relieve the pain Per*haps* a discussion of these matters may help to crystallize some of the issues

I am inclined to the view that when pain occurs in association with the contraction of a muscle it indicates a pathologic state or some secondary factor but not *the contraction per se* The voluntary contraction of the biceps muscle of the athlete

may be so extreme as to convert the muscle into an almost stony hard mass, but it doesn t hurt The contraction of the postpartum uterus is stony hard it also doesn't hurt In the fluoroscopic examination may be seen a sustained spastic contraction of the pylorus making it impossible for barium to pass yet this is usually quite painless The barium meal frequently discloses intense and long lasting spastic areas in the gastrointestinal tract, which produce no pain I am not aware of any satisfactory evidence that the normal contraction of a muscle is competent to produce pain This I believe, is the same as saying that a spasm of muscle in and of itself does not cause pain The pain is produced by other factors such as distortion of muscle, tearing of muscle fibers stretching of muscle, tension within a hollow viscus ischemia resulting from the sustained contraction of muscle and traction upon other structures by spasm as may occur in the case of the mesentery of the gastrointestinal tract

It is well known that skeletal muscle is sensitive to pain If you pinch it it hurts If you inject a little hypertonic solution into the skeletal muscle it may cause very severe pain These do not involve muscle contraction

A skeletal muscle which is exercised violently develops pain, not as the result of the contraction but in all probability, as the result of the accumulation of metabolites or as the result of muscle injury

Ischemia per se in muscles does not readily produce pain One can completely occlude the circulation to the arm and the arm will remain painless for a long time, unless the muscles are made to contract during the ischemia in which case the pain producing metabolites accumulate

The sudden violent cramp in the calf muscles which nearly throws a patient out of bed with excruciating pain is not the result of a contraction but of distortion of the muscles, a part of the muscle contracts violently, producing pulling and tearing effects upon the rest of the muscle This is not a case of

Management of Pain Due to Muscle Spasm

Dr. Harry Gold: The conference today is on the subject of the relief of pain which arises in association with the contraction of muscle. In some respects the problems here are similar to those of pain arising in other structures. Central analgesic agents such as morphine, codeine, demerol, and salicylates relieve pain in muscles as they do other forms of pain. Muscle pain, however, also presents some special problems in therapy. Drugs are used in the case of muscle pain not only to reduce perception of pain in the brain centers but to attempt to relax the muscle presumably for the purpose of eliminating the source of the painful impulse. The term "muscle spasm" is often applied in relation to these problems, and the drugs employed for the relief of such painful states are classified as antispasmodic agents.

The conditions are numerous; namely, the pain of coronary artery disease, peptic ulcer, spastic colon, biliary colic, renal colic, intermittent claudication, menstrual pain, labor pain, and pain in various disorders of the skeletal muscles.

I am not sure that we are altogether clear on what is happening in the so-called spastic muscle which gives rise to pain, and how we expect the drugs to act in order to relieve the pain. Perhaps a discussion of these matters may help to crystallize some of the issues.

I am inclined to the view that when pain occurs in association with the contraction of a muscle, it indicates a pathologic state or some secondary factor, but not the [illegible] per se. The voluntary contraction of the [illegible]

may be so extreme as to convert the muscle into an almost stony hard mass but it doesn t hurt The contraction of the postpartum uterus is stony hard it also doesn t hurt In the fluoroscopic examination may be seen a sustained spastic contraction of the pylorus making it impossible for barium to pass yet this is usually quite painless The barium meal frequently discloses intense and long lasting spastic areas in the gastrointestinal tract which produce no pain I am not aware of any satisfactory evidence that the normal contraction of a muscle is competent to produce pain This I believe is the same as saying that a spasm of muscle in and of itself does not cause pain The pain is produced by other factors such as distortion of muscle tearing of muscle fibers stretching of muscle tension within a hollow viscus ischemia resulting from the sustained contraction of muscle and traction upon other structures by spasm as may occur in the case of the mesentery of the gastrointestinal tract

It is well known that skeletal muscle is sensitive to pain If you pinch it it hurts If you inject a little hypertonic solution into the skeletal muscle it may cause very severe pain These do not involve muscle contraction

A skeletal muscle which is exercised violently develops pain not as the result of the contraction but in all probability as the result of the accumulation of metabolites or as the result of muscle injury

Ischemia per se in muscles does not readily produce pain One can completely occlude the circulation to the arm and the arm will remain painless for a long time unless the muscles are made to contract during the ischemia in which case the pain producing metabolites accumulate

The sudden violent cramp in the calf muscles which nearly throws a patient out of bed with excruciating pain is not the result of a contraction but of distortion of the muscles a part of the muscle contracts violently producing pulling and tearing effects upon the rest of the muscle This is not a case of

Management of Pain Due to Muscle Spasm

Dr Harry Gold The conference today is on the subject of the relief of pain which arises in association with the contraction of muscle In some respects the problems here are similar to those of pain arising in other structures Central analgesic agents such as morphine, codeine, demerol, and salicylates relieve pain in muscles as they do other forms of pain Muscle pain, however, also presents some special problems in therapy Drugs are used in the case of muscle pain not only to reduce perception of pain in the brain centers but to attempt to relax the muscle presumably for the purpose of eliminating the source of the painful impulse The term "muscle spasm" is often applied in relation to these problems, and the drugs employed for the relief of such painful states are classified as antispasmodic agents

The conditions are numerous, namely, the pain of coronary artery disease, peptic ulcer, spastic colon, biliary colic, renal colic, intermittent claudication menstrual pain, labor pain, and pain in various disorders of the skeletal muscles

I am not sure that we are altogether clear on what is happening in the so called spastic muscle which gives rise to pain and how we expect the drugs to act in order to relieve the pain Perhaps a discussion of these matters may help to crystallize some of the issues

I am inclined to the view that when pain occurs in association with the contraction of a muscle, it indicates a pathologic state or some secondary factor, but not the *contraction per se* The voluntary contraction of the biceps muscle of the athlete

ically, its benefits are still equivocal in cardiac pain, leg pains due to vascular disease such as arteriosclerosis or thromboangiitis obliterans, Raynaud's disease, and muscle pains of biliary and gastrointestinal origin. I am not sure of the reasons for the poor account this drug has given of itself. Perhaps we ought to consider much larger doses since as much as 1 Gm. in a single dose is said to be nontoxic.

Atropine is the standard antispasmodic agent used for the relief of pain arising in relation to the contraction of all smooth-muscle organs. It is usually employed either in the form of tablets of atropine sulfate or in the form of the tincture of belladonna. The usual dose is 0.5 to 1.0 cc. of the tincture which is equivalent to from 0.15 to 0.3 mg. (1/400 to 1/200 grain) of atropine. The physiologic basis for the use of atropine as an antispasmodic needs to be re-examined. Atropine acts by blocking the functions of the parasympathetic, but the gastrointestinal tract is notoriously resistant to this action of atropine so that, in animals, even after doses equivalent to 130 mg. for a man, electrical stimulation of the vagus still causes contraction of the gastrointestinal tract. There is further the fact that the gastrointestinal tract enjoys great autonomy, so that even when the vagus has been severed, the tract is capable of performing its usual motor activities and engages in motor perversions. These facts, therefore, indicate that on theoretic grounds atropine may be of no value at all in pain resulting from abnormal gastrointestinal motor functions. Several years ago Dr. Walter Bastedo made an interesting survey of the evidence concerning the action of atropine in gastrointestinal spasm. The indications are that it may not relieve spasm of the stomach. How, then, can we explain the fact that it sometimes relieves pain in the gastrointestinal tract? There are several possible mechanisms, but I would ask you to consider this one, namely, that atropine diminishes the tone and motility of the stomach and intestines. As the result of atropine administration, it may take as much as four times the normal length of

prevention or the relief of the pain of effort angina Although there is some experience indicating that a gallbladder or renal colic is sometimes relieved by a dose of nitrite, the nitrite is on the whole, not very satisfactory for these purposes I have often wondered why it is that its effect in cardiac pain should be so outstanding, and its effect in other conditions associated with so called muscle spasm should be so slight It may well be that in the case of coronary disease, it is only necessary to relax the vessels to relieve ischemia, however, in other types of smooth muscle pain, the chief problem is disturbed motility with the development of tensions and distortions which may continue even in the face of a degree of relaxation of a spastic area Differences in sensitivity of smooth muscles of different areas may be a factor

The xanthines, such as aminophylline, or theobromine and sodium acetate are fairly general smooth muscle-relaxing agents They are used with some success for the relaxation of the bronchial musculature in asthma They are used a great deal by oral administration for the control of the pain of angina pectoris. I doubt that they have much value by oral administration The intravenous dose of 0 25 Gm of aminophylline produces fleeting relaxation of the coronary vessels and is occasionally useful for that purpose In most of such cases if not in all, the nitrite under the tongue is equally, if not more effective

Papaverine relaxes smooth muscle It is said to exert its effect chiefly in hypertonic states allowing normal motor activity to continue, although there is indication that tone amplitude and frequency of contractions are diminished It is given in doses of 30 to 80 mg of the hydrochloride either orally intramuscularly, or intravenously The experimental results promise a great deal for this drug in the treatment of conditions requiring the relaxation of smooth muscle, and yet there is not a single clinical condition in which it has been used and in which the promises have been satisfactorily fulfilled Clin

terms, 'contraction" and "spasm," in connection with what you said about pain I would agree that a simple contraction of normal muscle does not cause pain Very strong electrical stimulation of normal muscle is not painful, but when we use the term spasm,' I think we bring in another connotation, a secondary factor, and that is the time factor When we say 'spasm," we have in mind a contraction which lasts over a period of time This probably results in local ischemia with ischemic pain I do not think the two words should be used without making that distinction

Dr Harold G Wolff That is all right if you wish to define them that way, but I did not think that spasm itself has necessarily anything to do with circulation

Dr Travell I think it connotes a time factor, that is, a prolonged contraction rather than a simple twitch There are experiments which show that in tetanic contraction the blood flow is markedly reduced

Dr Gold There is the fact to which I referred, that a cramp of the leg becomes painful almost the instant the contraction begins That pain couldn t be due to ischemia I believe the term 'spasm' would embrace this condition I am inclined to doubt that the time factor is important.

Are there any questions from the upper rows? I do not think we have yet found the combination for securing sufficient participation from the back rows Perhaps we ought to sit in the back row

Student I would like to ask Dr Wolff how pain arises when you inject hypertonic saline into a muscle

Dr Wolff I would assume that that is a direct stimulation of the pain end-organs by a chemical irritant I do not believe it has anything to do with the fact that it is in muscle It is simply bringing a chemical agent, a strongly hypertonic agent, in contact with the pain end-organ

Student There is no muscle spasm?

Dr Wolff There may be secondary muscle spasm which

fective relaxation of the stomach and also of the colon In comparison with atropine on the same subjects, it has been found that a dose of 50 mg intravenously causes the same effect as 0 6 mg of atropine, without the undesirable effects of the atropine

In spite of the strong indications of therapeutic value in the compounds which I have mentioned, the relief of pain in association with smooth muscle contraction is far from satisfactory. I wonder whether the inadequacy of all of these compounds may not be due chiefly to the brevity of their action

Calcium produces dramatic relief of lead colic and also in some cases, of renal and biliary colic after an intravenous dose of from 0 25 to 1 Gm of calcium chloride in a 5 per cent solution One needs approximately 3 times as much for an equivalent amount of calcium in the form of calcium gluconate The relief may be transient or may last for several hours The mechanism of its action remains obscure, for in animal experiments it fails to inhibit peristaltic movement

Tissue extracts are widely used to control nonstriated muscle pain They have had considerable vogue in treatment of pain of vascular disease Depropanex, a deproteinated pancreatic extract, has come in for a good deal of current attention in the treatment of leg pains in connection with peripheral vascular disease and intermittent claudication An intramuscular injection of 2 or 3 cc every other day has been stated to enhance the capacity of these patients for muscle activity without pain My own experience with it is not at all encouraging Is it not again chiefly a matter of brevity of action? An intravenous injection causes a vasorelaxation lasting 15 to 20 minutes That doesn't quite fit the accounts in the literature that patients will carry on better over longer periods of time as the result of an intramuscular injection a few times a week The use of tissue extracts as vasodilators is now a fairly old story It goes back about twenty years There is a large and optimistic literature, but the clinical results do not bear critical analysis

Dr Janet Travell I should like to ask a question about the

the relative ischemia When he tries to lie flat, the tension on these muscles produces sufficient discomfort to keep him awake He will often say that he is comfortable in bed when he lies with his knees drawn up Again, it is not the contraction of the muscles but the tension upon partially contracted muscles which hurts

When Dr Stimson discussed the treatment of poliomyelitis in one of our conferences, he mentioned the fact that patients are allowed to assume whatever position seems most comfortable, and the limbs are supported in those positions. In that way he avoids the stretching of the spastic muscle, since it is the stretching and not the spasm which is painful He suggested this as a means of treating the pain of muscle spasm while the Sister Kenny packs were being applied for the purpose of relaxing the spasm itself

I thought we might learn something about the relation between sudden muscle contractions and pain from the experience with the use of metrazol convulsions in mental disorders I discovered, however, that these patients develop a confusional state with loss of orientation just before the convulsions and are not in a position to give an account of whether the sudden muscle spasms caused pain although it is a fact that the total experience leaves them with sore muscles

Dr Walter Modell I have read accounts of convulsions due to strychnine poisoning The one by Stalberg and Davidson in the *J.A M A* (July 8, 1933) described a particularly long-drawn-out course Pain was not an outstanding symptom There was some back and neck pain, but the long and violent convulsions seemed to be associated with terror, a sense of suffocation, and anxiety, but not with pain The same is true of the muscle spasm of tetanus There is a good deal of sudden as well as sustained contraction of muscles with spasm in these cases and there is a great deal of pain in association with them The fact, however, that such patients may also show marked muscular spasticity, such as rigidity of the jaws which

pain, a maximum involuntary contraction, as occurs in spasm, would not cause pain unless there were something abnormal about the movement of the muscle, namely, something in the nature of abnormal pulls, distortions, and tensions?

Student How do you explain the fact that pain of muscle say of the leg, arises 24 hours after an unusual exercise whereas a muscle accustomed to the exercise does not develop pain?

Intern The usual answer to that is the P factor A blood pressure cuff, inflated on the arm so as to occlude the circulation, may be left in place for ½ to ¾ of an hour without pain but *pain develops rapidly when under those conditions the* muscle is made to contract. The difference is said to be due to the development of a metabolic pain factor It is, therefore, not the want of oxygen by itself or the want of any other factor in the blood which causes the pain The pain results from a factor which develops when a muscle contracts without adequate blood supply

Dr Travell In connection with sore muscles after unaccustomed exercise, I would point out that it is not contraction which hurts, but rather stretching of the muscle If you examine your own experience the next time you develop such muscle lameness, you will find that the muscle is tender to the touch, does not hurt when it shortens and causes pain when it is lengthened If it happens to be the calf muscles that are involved, *dorsiflexion of the foot is the movement which sets off* pain, if it is the hamstrings, straightening the knee sets off pain Sore muscles are often somewhat harder than normal muscles Their tone is high, and the stretch of contracted muscle gives rise to pain

Dr Gold In this connection we might bring together other types of experience As Dr Hansson pointed out, impairment of the circulation leads to contraction of the muscle The patient with occlusive vascular disease of the extremities often finds it one of his greatest difficulties to lie flat on his back The flexor leg muscles are in a state of high tone as the result of

of very frequent occurrence This is a condition which gives rise to a great many symptoms gaseous distention distress constipation loose bowel movements sometimes nausea sleeplessness and loss of weight A good many people feel that it is the most common cause of abdominal distress and some go so far as to say that if we could make a better diagnosis of this condition there would be less people operated on for chronic appendicitis It is found in both men and women There are many causes Some people feel that irritative cathartics are a very frequent cause A smaller number of cases are probably due to carbohydrate fermentative changes In these cases one finds acid stools that are mushy and contain bubbles of gas I think much rarer is the type due to excess protein putrefaction where one finds an alkaline stool Theoretically the treatment would be very simple if the intestinal flora could be changed We had an epidemic of acidophilous milk treatments a few years ago it was sold in all the drug stores Another cause almost as frequent as the use of irritative cathartics is the overexcitability of the vegetative nervous system due to stress and strain fatigue worry overwork family difficulties and the wear and tear of modern life in general In such cases people suffer from many persistent and varying gastrointestinal symptoms Abdominal examination is likely to reveal a ropelike colon on the left side There may be a boggy distended cecum You have probably all seen this condition which has now come to be called the spastic colon The X ray helps in the diagnosis At the end of twenty four hours a lot of chopped up discrete masses of barium are seen particularly on the left side and if one gives the patient a barium enema one finds there is a narrowed cecum

As to the treatment bed rest the application of heat where possible and diet are the important factors Probably one of the most important measures is a bland diet which at first cuts out raw fruits and raw vegetables iced drinks coffee irritants of all kinds and alcohol We all use the gastric sedatives $\frac{1}{50}$

I never heard that statement made by one from your department or similar departments before I agree with you absolutely I think that the effect of atropine administered in the usual clinical doses is due to the personality of the doctor who gives it

Dr Gold Dr Palmer, how do you manage the problems of pain with spasm in the gastrointestinal tract?

Dr Douglass Palmer There are several areas of spasm in the gastrointestinal tract A word about cardiospasm it is not a very frequent condition and it is necessary to distinguish it from cancer Mechanical dilatation is the only effective treatment In my experience, belladonna phenobarbital and other sedatives have been of no assistance in such a case Spasm in the rectum, or anal spasm is very common and extremely painful The diagnosis is frequently overlooked and the condition is often badly treated It is almost always due to a lesion generally a tear, just in the midline in the back of the anal opening The medical treatment of the pain is to keep the bowel movement soft using a lubricant, and to apply heat

In the case of pylorospasm, the treatment is directed at the cause If the cause be gastric ulcer, the treatment is that for ulcer The same treatment applies also if the primary condition is extrinsic pathology, such as gallbladder disease or chronic appendicitis In acute pylorospasm, rest is important the stomach should also be rested by withholding food particularly irritants coffee, alcohol, and cold drinks Heat applied to the abdomen is helpful, and opiates are sometimes necessary

Dr Gold As regards opiates in pylorospasm I would be inclined to think that the relief of pain is due to either the central suppression of the pain sense or suppression of the motility of the stomach, since spasm itself is likely to be increased by the opiate

Dr Palmer I shall say a few words about the treatment of spastic colon Spastic colitis, or the so-called irritable colon is

of very frequent occurrence. This is a condition which gives rise to a great many symptoms: gaseous distention, distress, constipation, loose bowel movements, sometimes nausea, sleeplessness, and loss of weight. A good many people feel that it is the most common cause of abdominal distress, and some go so far as to say that if we could make a better diagnosis of this condition, there would be less people operated on for chronic appendicitis. It is found in both men and women. There are many causes. Some people feel that irritative cathartics are a very frequent cause. A smaller number of cases are probably due to carbohydrate fermentative changes. In these cases one finds acid stools that are mushy and contain bubbles of gas. I think much rarer is the type due to excess protein putrefaction, where one finds an alkaline stool. Theoretically, the treatment would be very simple if the intestinal flora could be changed. We had an epidemic of acidophilous-milk treatments a few years ago; it was sold in all the drug stores. Another cause, almost as frequent as the use of irritative cathartics, is the overexcitability of the vegetative nervous system due to stress and strain, fatigue, worry, overwork, family difficulties, and the wear and tear of modern life in general. In such cases, people suffer from many persistent and varying gastrointestinal symptoms. Abdominal examination is likely to reveal a ropelike colon on the left side. There may be a boggy distended cecum. You have probably all seen this condition which has now come to be called the spastic colon. The X-ray helps in the diagnosis. At the end of twenty-four hours a lot of chopped-up discrete masses of barium are seen, particularly on the left side, and if one gives the patient a barium enema, one finds there is a narrowed cecum.

As to the treatment, bed rest, the application of heat where possible, and diet are the important factors. Probably one of the most important measures is a bland diet which, at first, cuts out raw fruits and raw vegetables, iced drinks, coffee, irritants of all kinds, and alcohol. We all use the gastric sedatives, $\frac{1}{60}$

I never heard that statement made by one from your department or similar departments before I agree with you absolutely I think that the effect of atropine administered in the usual clinical doses is due to the personality of the doctor who gives it.

Dr Gold Dr Palmer, how do you manage the problems of pain with spasm in the gastrointestinal tract?

Dr Douglass Palmer There are several areas of spasm in the gastrointestinal tract A word about cardiospasm it is not a very frequent condition and it is necessary to distinguish it from cancer Mechanical dilatation is the only effective treatment In my experience, belladonna phenobarbital and other sedatives have been of no assistance in such a case Spasm in the rectum, or anal spasm, is very common and extremely painful The diagnosis is frequently overlooked and the condition is often badly treated It is almost always due to a lesion generally a tear, just in the midline in the back of the anal opening The medical treatment of the pain is to keep the bowel movement soft, using a lubricant, and to apply heat

In the case of pylorospasm, the treatment is directed at the cause If the cause be gastric ulcer, the treatment is that for ulcer The same treatment applies also if the primary condition is extrinsic pathology, such as gallbladder disease or chronic appendicitis In acute pylorospasm, rest is important the stomach should also be rested by withholding food particularly irritants coffee, alcohol, and cold drinks Heat applied to the abdomen is helpful, and opiates are sometimes necessary

Dr Gold As regards opiates in pylorospasm I would be inclined to think that the relief of pain is due to either the central suppression of the pain sense or suppression of the motility of the stomach, since spasm itself is likely to be increased by the opiate

Dr Palmer I shall say a few words about the treatment of spastic colon Spastic colitis, or the so called irritable colon is

of very frequent occurrence This is a condition which gives rise to a great many symptoms gaseous distention distress constipation loose bowel movements sometimes nausea sleeplessness and loss of weight A good many people feel that it is the most common cause of abdominal distress and some go so far as to say that if we could make a better diagnosis of this condition there would be less people operated on for chronic appendicitis It is found in both men and women There are many causes Some people feel that irritative cathartics are a very frequent cause A smaller number of cases are probably due to carbohydrate fermentative changes In these cases one finds acid stools that are mushy and contain bubbles of gas I think much rarer is the type due to excess protein putrefaction where one finds an alkaline stool Theoretically the treatment would be very simple if the intestinal flora could be changed We had an epidemic of acidophilous milk treatments a few years ago it was sold in all the drug stores Another cause almost as frequent as the use of irritative cathartics is the overexcitability of the vegetative nervous system due to stress and strain fatigue worry overwork family difficulties and the wear and tear of modern life in general In such cases people suffer from many persistent and varying gastrointestinal symptoms Abdominal examination is likely to reveal a ropelike colon on the left side There may be a boggy distended cecum You have probably all seen this condition which has now come to be called the spastic colon The X ray helps in the diagnosis At the end of twenty four hours a lot of chopped up discrete masses of barium are seen particularly on the left side and if one gives the patient a barium enema one finds there is a narrowed cecum

As to the treatment bed rest the application of heat where possible and diet are the important factors Probably one of the most important measures is a bland diet which at first cuts out raw fruits and raw vegetables iced drinks coffee irritants of all kinds and alcohol We all use the gastric sedatives $\frac{1}{50}$

I never heard that statement made by one from your department or similar departments before. I agree with you absolutely. I think that the effect of atropine administered in the usual clinical doses is due to the personality of the doctor who gives it.

Dr. Gold: Dr. Palmer, how do you manage the problems of pain with spasm in the gastrointestinal tract?

Dr. Douglass Palmer: There are several areas of spasm in the gastrointestinal tract. A word about cardiospasm: it is not a very frequent condition and it is necessary to distinguish it from cancer. Mechanical dilatation is the only effective treatment. In my experience, belladonna, phenobarbital, and other sedatives have been of no assistance in such a case. Spasm in the rectum, or anal spasm, is very common and extremely painful. The diagnosis is frequently overlooked and the condition is often badly treated. It is almost always due to a lesion, generally a tear, just in the midline in the back of the anal opening. The medical treatment of the pain is to keep the bowel movement soft, using a lubricant, and to apply heat.

In the case of pylorospasm, the treatment is directed at the cause. If the cause be gastric ulcer, the treatment is that for ulcer. The same treatment applies also if the primary condition is extrinsic pathology, such as gallbladder disease or chronic appendicitis. In acute pylorospasm, rest is important; the stomach should also be rested by withholding food, particularly irritants, coffee, alcohol, and cold drinks. Heat applied to the abdomen is helpful, and opiates are sometimes necessary.

Dr. Gold: As regards opiates in pylorospasm, I would be inclined to think that the relief of pain is due to either the central suppression of the pain sense or suppression of the motility of the stomach, since spasm itself is likely to be increased by the opiate.

Dr. Palmer: I shall say a few words about the treatment of spastic colon. Spastic colitis, or the so-called irritable colon, is

of very frequent occurrence This is a condition which gives rise to a great many symptoms gaseous distention distress constipation loose bowel movements sometimes nausea sleeplessness and loss of weight A good many people feel that it is the most common cause of abdominal distress and some go so far as to say that if we could make a better diagnosis of this condition there would be less people operated on for chronic appendicitis It is found in both men and women There are many causes Some people feel that irritative cathartics are a very frequent cause A smaller number of cases are probably due to carbohydrate fermentative changes In these cases one finds acid stools that are mushy and contain bubbles of gas I think much rarer is the type due to excess protein putrefaction where one finds an alkaline stool Theoretically the treatment would be very simple if the intestinal flora could be changed We had an epidemic of acidophilous milk treatments a few years ago it was sold in all the drug stores Another cause almost as frequent as the use of irritative cathartics is the overexcitability of the vegetative nervous system due to stress and strain fatigue worry overwork family difficulties and the wear and tear of modern life in general In such cases people suffer from many persistent and varying gastrointestinal symptoms Abdominal examination is likely to reveal a ropelike colon on the left side There may be a boggy distended cecum You have probably all seen this condition which has now come to be called the spastic colon The X ray helps in the diagnosis At the end of twenty four hours a lot of chopped up discrete masses of barium are seen particularly on the left side and if one gives the patient a barium enema one finds there is a *narrowed cecum*

As to the treatment bed rest the application of heat where possible and diet are the important factors Probably one of the most important measures is a bland diet which at first cuts out raw fruits and raw vegetables iced drinks coffee irritants of all kinds and alcohol We all use the gastric sedatives 1/50

I never heard that statement made by one from your department or similar departments before I agree with you absolutely I think that the effect of *atropine administered in the* usual clinical doses is due to the personality of the doctor who gives it

Dr Gold Dr Palmer, how do you manage the problems of pain with spasm in the gastrointestinal tract?

Dr Douglass Palmer There are several areas of spasm in the gastrointestinal tract A word about cardiospasm it is not a very frequent condition and it is necessary to distinguish it from cancer Mechanical dilatation is the only effective treatment In my experience, belladonna phenobarbital and other sedatives have been of no assistance in such a case Spasm in the rectum, or anal spasm is very common and extremely painful The diagnosis is frequently overlooked and the condition is often badly treated It is almost always due to a lesion generally a tear, just in the midline in the back of the anal opening The medical treatment of the pain is to keep the bowel movement soft using a lubricant and to apply heat

In the case of pylorospasm the treatment is directed at the cause If the cause be gastric ulcer, the treatment is that for ulcer *The same treatment applies also if the primary* condition is extrinsic pathology, such as gallbladder disease or chronic appendicitis In acute pylorospasm rest is important the stomach should also be rested by withholding food particularly irritants, coffee, alcohol and cold drinks Heat applied to the abdomen is helpful, and opiates are sometimes necessary

Dr Gold As regards opiates in pylorospasm I would be inclined to think that the relief of pain is due to either the central suppression of the pain sense or suppression of the motility of the stomach since spasm itself is likely to be increased by the opiate

Dr Palmer I shall say a few words about the treatment of spastic colon Spastic colitis, or the so-called irritable colon is

tion to mean that peristaltic waves at the onset, with distention cause pain, which is later followed by subsidence of pain due to the subsidence of the peristaltic waves The pain disappears because of transient paralysis of the bladder

It is not uncommon, following ureteral catheterization in which no pathologic condition is found, that the patient has an acute renal colic as the result of the manipulation One possible interpretation is that the trauma causes spasm and that the spasm may act, as in the case of the stone, to produce pain related to hypermotility or hyperperistalsis

A renal colic will invariably cause spasm of the abdominal muscles namely, the transversalis, and internal and external oblique muscles which will stay in a state of contraction This will result in pain in this muscle the same as in the case of contraction of any skeletal muscle

In my clinical experience, the so called antispasmodics such as atropine, syntropan, and spasmalgin have had no effect in cases of severe renal colic The only drugs which I know will relieve pain in the urinary tract caused by spasm of the smooth muscles are the opiates and their derivatives In healthy adult patients 30 mg may be given and this repeated in ½ hour if necessary Tincture of hyoscyamus in combination with citrates is only of value in so far as the pH of the urine is altered. Calcium gluconate given intravenously has been, in my experience, of no benefit in renal colic

Dr Gold Dr Shorr does the pain associated with the contraction of the uterus present any special problems?

Dr Ephraim Shorr I think we remain particularly uncertain and insecure in our treatment of pain of uterine origin Fundamentally, this is related to the question which Dr Gold raised concerning the relation between muscle spasm and pain

There are some very good accounts of the behavior of the uterus during the sexual cycle During menstruation there are contractions, relatively slow and of moderate amplitude,

grain of atropine sulfate, or combinations of atropine or belladonna with phenobarbital. Oil-retention enemas which are retained overnight are sometimes useful.

Dr. Gold: Could we hear from Dr. McLellan about treatment of pain in disorders of the genitourinary tract?

Dr. Allister M. McLellan: Clinical observation indicates that pain from the kidney, pelvis, bladder, and ureter is due to hypermotility of the smooth muscle when it is distended and peristaltic waves are present. If these organs become overdistended sufficiently to suppress peristaltic activity, the pain disappears. An obstruction in the ureter per se, such as by a stone in the ureter, does not cause clinical renal colic, although some vague discomfort may be present. A stone in the kidney pelvis may cause slight discomfort in the costovertebral angle, and a stone in the ureter may give vague discomfort along the outer border of the rectus muscle from the umbilicus to the suprapubic region, depending upon the location of the stone from the ureteropelvic junction to the suprapubic region. I may cite the case of a patient who had a single kidney with an infected, greatly dilated ureter containing a large stone. The first symptoms of obstruction in her case were anuria and vomiting. The patient would readily recognize these clinical symptoms and would come to the office asking that a catheter be passed to dislodge the stone. With this, symptoms would disappear. At no time was there pain referable to the kidney. I would presume that no peristalsis was present in her case. It is a common observation that a ureteral stone may cause acute colic at the onset. The pain then completely subsides, and an intravenous pyelogram taken later will show a nonfunctioning kidney. I assume this to represent a state in which the peristaltic waves have subsided, resulting in a painless pathologic condition.

An overdistended bladder at the onset is always painful but if it is allowed to persist, or if morphine is given to mask the symptoms, pain will disappear. Again I interpret this observa-

tion to mean that peristaltic waves at the onset, with distention cause pain which is later followed by subsidence of pain due to the subsidence of the peristaltic waves The pain disappears because of transient paralysis of the bladder

It is not uncommon, following ureteral catheterization in which no pathologic condition is found, that the patient has an acute renal colic as the result of the manipulation One possible interpretation is that the trauma causes spasm and that the spasm may act, as in the case of the stone, to produce pain related to hypermotility or hyperperistalsis

A renal colic will invariably cause spasm of the abdominal muscles namely, the transversalis and internal and external oblique muscles, which will stay in a state of contraction This will result in pain in this muscle the same as in the case of contraction of any skeletal muscle

In my clinical experience, the so called antispasmodics, such as atropine, syntropan, and spasmalgin have had no effect in cases of severe renal colic The only drugs which I know will relieve pain in the urinary tract caused by spasm of the smooth muscles are the opiates and their derivatives In healthy adult patients, 30 mg may be given and this repeated in ½ hour if necessary Tincture of hyoscyamus in combination with citrates is only of value in so far as the pH of the urine is altered. Calcium gluconate given intravenously has been, in my experience, of no benefit in renal colic

Dr Gold Dr Shorr, does the pain associated with the contraction of the uterus present any special problems?

Dr Ephraim Shorr I think we remain particularly uncertain and insecure in our treatment of pain of uterine origin Fundamentally, this is related to the question which Dr Gold raised concerning the relation between muscle spasm and pain

There are some very good accounts of the behavior of the uterus during the sexual cycle During menstruation there are contractions, relatively slow and of moderate amplitude,

which persist throughout the period of menstruation. The uterus is firm, and the firmness is general. Then follows a period of relative quiescence until the preovular spurt in the growth of the follicle; in the 4 or 5 days associated with the rapid development of the follicle and the increased excretion of estrogens, there is a very great increase in the amplitude and frequency of the contractions. This is followed by another period of quiescence, and then 1 or 2 days premenstrually there is again an increase in the amplitude, giving rise to the menstrual characteristics of the uterine contractions. From the analysis of hormonal response of uteri which have been deprived of their endogenous hormones, we know that the estrogenic hormone increases the activity of the uterus, the amplitude and the frequency of its contractions, and renders it much more susceptible to the action of the oxytocic principle of the posterior pituitary, and that progestin has the opposite effect.

We can place women into various categories. There are those to whom these episodes of increased contractility are unassociated with any awareness of the uterine contractions; then, there are all gradations between this group and the women in whom menstruation produces almost intolerable cramps, associated with so many other distressing phenomena: nausea, vomiting, and all the bizarre symptoms that may be seen in extreme cases. There are some women who are very definitely aware of ovulation, and that there is a physiologic basis for their awareness is evident from the nature of the contractions throughout this period.

Is there any difference in the contractions of the uterus of women who have dysmenorrhea from those who have painless menstruation? The best studies I know of, which have been made by the insertion of balloons at the time of menstruation, have indicated no difference whatsoever in the force or in the frequency of the uterine contractions, so that we cannot differentiate the two types on the basis of the contraction of the

uterus The difference lies in their response to the contraction.

A great variety of therapeutic procedures have been instituted to deal with the problem of dysmenorrhea Of course, the simplest one is to use the analgesics, starting with the mild ones and going to codeine, and finally to morphine, but that seems to avoid contact with the hormonal influences that we do know definitely alter the rate and degree of contraction A variety of hormonal procedures have been adopted which are varyingly successful

There has been an attempt to classify women with dysmenorrhea into two types one, those with a hypoplastic uterus, to whom estrogenic hormone therapy is given, and the other, those with a normal type of uterine contractions, in whom the depressing effects of the progestinal hormones on uterine contraction have been utilized I find that those distinctions are not very clear cut, and that the response is irregular to both hormonal regimens which are usually started a few days premenstrually and are continued throughout menstruation

There is still another regimen, adopted by Sturgis and Albright, and others, which is fairly successful Starting rather early in the cycle, say, about the sixth day, one gives large doses of estrogenic hormone, 10,000 rat units every 3 days for 6 doses The succeeding period is frequently less painful or may be entirely free of pain This is an end achieved apparently not without cost, because both assays of progestin at that time and biopsies indicate that we have very seriously interfered with normal menstrual function My own feeling is that these measures are justified in those women whose disability is so severe as to become a serious problem

I would like to present another point of view which seems to be borne out by evidence not only in this particular field of pain but in so many others namely, that of the emotional state of the patient You will recall that the uterine contractions in dysmenorrhea are the same as in women with painless menstruation I think one can succeed very well in picking out,

before one has gone very far into the history, those women who are likely to have dysmenorrhea They can be distinguished from those who are likely to have painless menstruation The state of tension, the degree of neurosis, the state of anxiety, and the particular stress seem to be the *conditioning factors* which give rise to a pain reaction in a patient having an apparently perfectly normal type of contraction There are, of course those patients in whom the pain is so severe that something must be done prior to any long term therapy, but the aim of any treatment should be a more general approach to the problem of dysmenorrhea on the basis of personality factors It is not one for long range management with drugs

Dr Wolff Do you think the estrogen affects the contraction pattern of the uterus or the patient's reaction to it?

Dr Shorr I am not certain, of course but I am inclined to the belief that the effect on the patient's reaction is the most important factor

Dr Cattell Since your formulation would give some importance to factors influencing the central nervous system, would you not use sedatives on occasion?

Dr Shorr Yes, indeed

Dr Wolff How about alcohol and aspirin?

Dr Shorr Brandy and aspirin are favorites with women in these circumstances

Dr Gold I am inclined to think that the factor of pull, distortion, or tension is not ruled out as a cause of the pain in the dysmenorrheic woman A normal pattern of contractions might very well produce no tortions in one woman while producing painful pulls in another The effect might well depend for example, on the relation of the uterus to adjacent structures which might vary from person to person

I don t wish to take issue with the notion that the psychologic constitution of women is a very important factor I wish merely to stress the fact that pain which arises in relation to a strong muscle contraction need not arise from the contraction

itself but from the effect of the contraction on related or adjacent structures The difference between the normal and dysmenorrheic woman may lie in these relations rather than in the pattern of the contraction of the uterus itself This is precisely analogous to what we have already mentioned in connection with pylorospasm What causes the hurt is not the spasm itself but the related movements of the stomach giving rise to tensions and tortions

Dr Shorr There can be no doubt that frequent instances of dysmenorrhea are relieved by the relief of stress A vacation often does it

There is one other condition I would like to point out because I think it is overlooked more often than it should be and that is the presence of endometriosis I do not qualify as a gynecologist but I have had some experience with that particular form of dysmenorrhea Not infrequently such women complaining of dysmenorrhea which differs in no degree or specific quality from ordinary dysmenorrhea are treated for years without the diagnosis of endometriosis Those patients can be relieved by surgery as you know but they may also be relieved if the endometrial deposits are not too extensive by the use of androgens Androgens produce two effects One, they cause the endometrium to involute two in proper doses they prevent the next discharge of gonadotropic stimuli from the pituitary so that a menstruation is missed and during that period there is a regression of the endometrium It so happens that the ectopic endometrium is much less resistant to such temporary omissions of hormonal stimulation than that of the uterus and not infrequently one or two such courses with androgenic therapy result in marked or even complete relief of pain The diagnosis of endometriosis is always to be borne in mind

Dr Gold Dr Hansson I believe that one of the major problems in physical medicine is to relieve muscle pain Would you tell us briefly what you do?

Dr Hansson Spasm of skeletal muscle represents merely an increased tone of the muscle The action current shown by the electromyogram is the same for a muscle spasm as it is for a normal muscle during contraction We encounter pain in the skeletal muscles in a wide variety of situations the spasticity of cerebral hemorrhage, local conditions such as myositis as in the case of the trapezius muscle or wryneck, spasm in association with fractures or pathologic states around the joints, spasm resulting from impaired circulation as in ischemic contracture, skeletal muscle spasm due to general conditions as in meningeal irritation, and the spastic muscles of poliomyelitis

There have been some interesting experiments in recent years relating skeletal muscle spasm to acetylcholine Prostigmine has been used for the relief of muscle spasm in poliomyelitis and in arthritis on the basis of the assumption that the resulting increase in acetylcholine at the neuromuscular junctions will relax the muscle Some writers have made a good deal of this medication although our own experience has not been nearly as encouraging

Spasm in the skeletal muscle will usually respond to the application of heat by means of electrical currents The heat may be either external or internal or a combination of the two In regard to external heat, there is some question of a choice between moist heat and dry heat I believe that both do essentially the same thing physiologically

Visitor Isn t it true that the application of heat is probably the most valuable therapeutic measure in the treatment of skeletal or smooth muscle pain? Is not the return of the circulation to the affected parts as the result of heat application the reason for the cessation of the pain?

Dr Hansson I think that the pain of skeletal muscle is often due to impaired circulation, and that the relief is due to improvement in the circulation

Dr Gold I would like to ask Dr Hansson how he decides

whether he should use dry or moist heat for the relief of pain associated with skeletal-muscle spasm.

Dr. Hansson: This is a very practical question. As I stated, physiologically, the two are the same. However, from the standpoint of the practical application, moist heat presents certain advantages. In the case of dry heat, we usually use an incandescent lamp, and the heat increases gradually as its application continues. There is, therefore, a danger of overheating. Furthermore, the heat strikes only that part of the body on which it is focused; the areas to the side or the back fail to get any exposure. On the other hand, in the case of moist heat, usually applied by moist packs, the maximum amount of heat is present at the start and with time tends to cool off toward normal. There is, therefore, little danger of burning, and the further advantage of being able to distribute the heat all around an extremity.

Dr. Gold: Is there anything else that the physiotherapist does to relieve pain of skeletal-muscle spasm besides applying heat?

Dr. Hansson: Yes, indeed There are several measures which are used in physical medicine in addition to heat to promote relaxation of muscles Gentle massage, including stroking or effleurage, is often quite effective. We sometimes use iontophoresis with members of the histamine group introduced into the skin by means of electrical currents. Progressive relaxation exercises requiring the special technic of Dr. Edmund Jacobson, of Chicago, are beneficial in hemiplegia or other cerebral spastic states. The continuous bath as commonly used by the psychiatrists to quiet the excited patient has the effect of relaxing skeletal muscle; in this case it may be that the heat is responsible. Another measure which indirectly relaxes skeletal muscle is cold as applied to reduce the distention of a joint capsule or hollow sac, since the pain of the distention tends to cause reflex spasm of the skeletal muscle around the joint.

Visitor Could we have some advice as to how to treat the acute muscle cramp in the legs which often comes on while the patient is in bed at night? What should the doctor do to relieve it, or what can the patient himself be instructed to do?

Dr. Hansson I believe that most of these cramps are the result of a circulatory deficiency due either to a systemic lowering of the blood pressure when the patient is at rest or to a local deficiency in the circulation caused by vascular disease of the extremity Therefore, the treatment should be directed toward increasing the circulation This can be done by the application of a hot pack or electric pad, and also by having the patient hang his legs over the side of the bed and exercise—alternately flex and extend—the ankles and toes, or get out of bed, which he usually does instinctively, and stand or walk These measures usually relieve the cramps A dose of 5 or 10 grains of aspirin may be helpful. Quinine has been used for relaxing skeletal muscles A dose of 5 or 10 grains of quinine sulfate may also be tried.

Dr. Gold Dr Travell, you have had some experience with the management of skeletal muscle pain Would you tell us something about what you do?

Dr. Travell I have been particularly interested in the treatment of muscle pain by means of local infiltration of procaine into the so called "trigger zones" in the skeletal muscles The pain in the cases to which I shall refer is usually of obscure origin, and there is no causative diagnosis They include such syndromes as the frozen shoulder, low back pain, stiff neck, tennis elbow, and stiff and painful knees A careful examination shows that the pain is associated with spasm of the muscles resulting in limitation of motion In these cases every kind of laboratory examination may be negative, X rays of the bony structures, blood count, blood sedimentation rate, blood chemistry, and the spinal fluid may show no significant abnormalities The neurologic examination is also negative Those muscles which cross the joints at which limitation is observed

show localized areas of deep tenderness Pain is elicited when the tender muscle is stretched If there is pain when at rest as well as when in motion, some spot in an appropriate muscle can almost always be found, firm pressure on which reproduces or increases the pain This is called a trigger zone and represents an abnormal area within the muscle from which pain is referred to areas often located at a considerable distance from the trigger zone For instance, in patients with low-back pain, trigger zones in the gluteal muscles frequently give rise to pain radiating down the back and outer side of the leg as far as the ankle, resulting in the clinical syndrome of sciatica

In the management of these patients, briefly, this is what I do After examination of the muscles for tender spots, restricted motion, pain on reclining, the setting off of referred pain by pressure, and after ruling out other types of pathology, I infiltrate as many trigger areas as I can find, or as the patient will tolerate I generally use a 0 5 per cent to 0 25 per cent solution of procaine hydrochloride in physiologic saline, which must be pyrogen free There is no epinephrine in the solution It is not necessary to infiltrate the skin When the needle penetrates into a trigger zone, this section of the muscle usually can be seen or felt to twitch, and the patient experiences a sharp radiating pain which may build up in the reference zone during several seconds or even minutes, spreading in waves from one part of the reference area to another This suggests a mechanism of pain reference in the central nervous system based on a ' reverberating neurone circuit ' as postulated years ago by Hinsey to explain motor after-discharges

But to come back to the patient When a trigger area is found, the needle is moved rapidly back and forth in this region until the whole area has been ' peppered ' with the solution and the patient no longer feels the movement of the needle or the introduction of the fluid The trigger area in a

large muscle mass seems to be a globular spot about 1 cm. in diameter, and, in a small muscle, only 2 or 3 mm. in diameter. In making the injection, it is not necessary to retract on the plunger of the syringe to determine whether the point of the needle is located in a blood vessel, because during the injection the needle is kept in motion so that no more than a drop or two is introduced at any one point, and because the solution of procaine hydrochloride used is so dilute. The total amount of the solution injected in attempting to abolish any single trigger zone ranges usually from about 2 to 5 cc.

It should be emphasized that the infiltration of an active trigger area should be repeated until deep tenderness at that site is abolished, even though several trials are necessary. The incomplete blocking of trigger areas is probably responsible for most of the afterpain and some of the failures from this type of treatment. Increased pain for a day or two following the treatment also results when the reference area, instead of the trigger zone, is infiltrated.

Another reason for a poor end result is that the search for additional trigger areas is not sufficiently persistent. When marked relief from pain and disability has been secured for a period of time and the pain subsequently recurs, one should first reinvestigate the trigger areas already injected, but it will generally be found that the trigger zones located elsewhere than in the muscles already treated are now responsible for the recurrence of pain. This is usually confirmed by a change in the site of pain.

Sometimes disagreeable but not dangerous reactions to procaine hydrochloride are encountered, such as light-headedness, dizziness, drowsiness, or motor incoordination. The patient feels as if he had a strong cocktail. These effects wear off within 15 or 20 minutes and are due to actions of the drug on the central nervous system. They are much less noticeable if the treatment is given with the patient lying down. Some patients apparently have a true idiosyncrasy to procaine hydrochloride,

with immediate collapse symptoms which can be counteracted by epinephrine but this is infrequent and usually may be anticipated by a careful history for allergies

A rare reaction is the delayed appearance of convulsive movements or convulsions 1 or 2 hours after the procaine I have seen this once in about 500 patients treated by this technic This reaction may be prevented or abolished by the barbiturates and as a precaution and also to make the patient less apprehensive I often give pentobarbital sodium 0 1 Gm by mouth 10 or 15 minutes to ½ hour before the treatment is begun I also limit the amount of procaine used at the first visit to 100 mg and increase it gradually if need be at later visits

In patients with a known allergy to procaine I use plain physiologic saline solution for infiltration I have now quite a group of patients who have been treated with physiologic saline alone from start to finish and it is my impression that the results are just as good as when procaine is used The addition of procaine to the solution unquestionably makes the injection more pleasant to the patient in that the pain set off by needling the trigger zone is less intense and of shorter duration than when saline alone is used

Now as to the mechanism of the relief of pain by this kind of treatment The most puzzling fact is that a procedure with such temporary pharmacologic effects produces in many instances long lasting or permanent relief For instance if the pain is of short duration of the order of 2 or 3 weeks 1 treatment usually suffices If it has been present for periods of months and even years marked relief is often secured after 3 or 4 treatments given at weekly intervals This suggests that the spasm of the muscles is a functional disorder and that the infiltration has in some way interrupted a vicious cycle

The relief of pain cannot be the result of a simple local anesthetic action of procaine as I once thought because saline is equally effective Nor is the relief due to purely psychic ef

fects of the treatment, since infiltrating *non*tender areas of muscle, a procedure which does not elicit any spread of pain, is quite ineffective in relieving the symptoms.

Dr. Nolton Bigelow has pointed out to me that Gellhorn's experiments offer the best explanation of this enigma of the relief of pain by the local infiltration of trigger zones. Gellhorn found that pain induced by the ischemic contraction of a muscle temporarily abolishes the deep tendon reflex of that particular muscle, whereas ischemia alone, in the absence of pain, has no such effect. One must conclude that afferent pain impulses in some way block reflex pathways, possibly by using up some chemical substances necessary for the transmission of the impulse. In the patient in question, the intense discharge of pain impulses, set off by infiltrating the trigger area, would serve as the essential factor in breaking the vicious cycle and relaxing muscular spasm.

Dr. Gold: I take it, then, that you believe that the thing that relieves the muscle pain is a painful stimulus striking the trigger area rather than the anesthetization of the trigger area, do you not?

Dr. Travell: Yes, I believe that is the explanation.

SUMMARY

Dr. Gold: The management of pain associated with muscle spasm was the subject of the conference today. This problem is not an exclusive one. Several specialties have a stake in it—pharmacology, neurology, psychiatry, orthopedics, gastroenterology, urology, endocrinology, physical medicine, and others. Some special aspects of pain with muscle spasm as it arises in these various fields were explored.

Relatively little was said about the cause of the muscle spasm itself. Concerning this, there are many suggestions in the literature—infection, fatigue, anoxia, toxic factors, neuritis, vitamin deficiencies, alkalosis, hypocalcemia, and others.

Neostigmine has been found to increase muscle contraction

and promote spasm, while others have made use of it for the purpose of relaxing muscle There is an interesting contribution to the subject of muscle cramps in the recent studies of van Wagtendonk and his collaborators, who isolated a dietary factor in raw cream which cures muscle stiffness in animals

The discussion, however, turned around a different question Whether the contraction of muscle per se is competent to give rise to a painful stimulus The view was expressed that the contraction of muscle does not cause pain, and that when pain arises in association with muscle contraction or spasm, it is due either to ischemia resulting from prolonged contraction, or pulls, tortions, and distentions arising in connection with long or brief contractions Many illustrations were cited of the fact that muscle spasm does not necessarily give rise to pain It was indicated that in the relief of pain associated with muscle spasm there may be two modes of attack—one, to relax the spasm itself, and two, to control those factors giving rise to pulls, tensions, and distortions of muscle and adjacent structures There was some discussion of several drugs commonly employed for the control of pain associated with spasm in smooth and in skeletal muscle, such as atropine, novatropine, syntropan, trasentin, opiates, aspirin, neostigmine, quinine, and procaine Their mechanism of action, uses, and limitations received some attention.

Treatment of Thrombophlebitis

Dr Wm DeWitt Andrus The subject of the conference today is the treatment of thrombophlebitis This disease is a source of a great deal of worry and annoyance to clinicians, and is the cause of a great many tragedies It is encountered in both medical and surgical cases It is, therefore, of interest to all of us The discussion will be opened by Dr Irving Wright

Dr Irving S Wright I may preface my remarks by saying that the treatment of thrombophlebitis constitutes one of the most controversial subjects in the field of medicine today, just as it has for the last fifteen years We have tried to steer a course between the two extremes of prejudice and resistance to new advances in therapy on the one hand and on the other, of overenthusiastic acceptance of therapeutic measures which have not seemed especially sound Such a course has been quite difficult Numerous forms of treatment have been suggested, many of which have enjoyed only temporary popularity There was, for example, the plan of immediate ambulation without any supplementary measures such as venous ligation or anticoagulant therapy The use of leeches was widely advocated abroad for many years and to a lesser degree in this country Lumbosacral block was advocated as a cure, and although it has proven to be of value in some patients it is no longer regarded as a cure

Thrombophlebitis is not a single disease There has been an unfortunate tendency in recent years to confine the scope of discussions on this subject to thrombophlebitis in postoperative patients, and further, to thrombophlebitis of the lower

extremities There are many important types of the disease There is one due to chemical irritants such as arsphenamine and concentrated vitamin C solutions Another type is due to chronic trauma for example persistently tying shoe laces too tightly over the arch of the foot There is suppurative thrombophlebitis in which the infection extends from a nearby abscess or severe infection There is thrombophlebitis associated with various blood dyscrasias such as polycythemia and leukemia There is the type associated with thromboangiitis obliterans Frequently it is the presenting problem in thromboangiitis obliterans the underlying disease escaping recognition by the physician There is also thrombophlebitis migrans which is relentless and frequently spreads to all parts of the venous system ending fatally in a high percentage of patients It is evident that the treatment of thrombophlebitis cannot be reduced to a simple routine The treatment of each patient must be decided on the basis of the etiologic factors and the presenting pathologic changes

In any large hospital the largest number of cases of thrombophlebitis are secondary to surgical or obstetrical procedures but in office practice and the practice of internal medicine one frequently sees cases due to the other causes

The difference between thrombophlebitis and phlebothrombosis has received considerable emphasis perhaps more than it deserves It is true that thrombi in phlebothrombosis are not fixed firmly to the walls of the veins during the early days when there is little inflammatory reaction In most instances as time elapses they become firmly fixed and cannot be distinguished pathologically from those in thromboses due to thrombophlebitis The important matter is that venous thromboses except those due to thromboangiitis obliterans are capable of producing emboli The silent thromboses frequently produce emboli as devastating as the ones that are easy to recognize It is impossible to predict whether or not a patient who has a thrombophlebitis in the legs is going to have a

fatal pulmonary embolus; therefore, all thrombophlebitis must be regarded as serious and potentially fatal if steps are not taken to prevent the formation of emboli.

Let us consider briefly the several therapeutic measures which have long been studied, although in the case of some of them considerable doubt still prevails regarding the best procedure. I believe there is a fairly universal agreement today that, in the case of a patient with thrombophlebitis of the lower extremity, with edema, elevation of the extremity is helpful in reducing the edema to a minimum. To keep the affected extremity in a dependent position or at the level of the body is of no therapeutic value and may actually be harmful.

Whether heat or cold should be applied to such patients has long been debated. The consensus at present seems to favor heat, if properly applied. I am not sure that we know how to apply it properly. The technic described by Barker is now most acceptable. The affected extremity is carefully covered with a thin layer of petrolatum or similar substance to prevent maceration of the skin, and a moist, hot pack is applied. This may be in the form of turkish towels dipped in hot water, wrung out and laid loosely around the extremity, which is then covered with a rubber blanket and surrounded by hot water bags. The hot pack is kept on for 20 out of 24 hours, allowing 4 hours for aeration and drying of the skin. In severe cases with marked edema, both lumbosacral sympathetic block and hot packs may be used simultaneously. The application of hot packs to an extremity immediately after lumbosacral block seems to prolong the vasodilating effect of the block, reducing vascular spasm and permitting more free drainage.

The matter of activity versus rest has long been debated, and it is still unsettled. There are some who believe that one should wrap a bandage tightly around an affected leg and instruct the patient to walk 40 to 60 blocks a day, if there are

no symptoms. I have seen some very poor results from this form of therapy. There are those who believe in keeping the patient at complete rest in bed until signs of the disease have completely subsided, as determined by the return to normal of the sedimentation rate, blood count, heart rate, and temperature. A middle course between these two extremes seems to be the present tendency. Those who have been using anticoagulant therapy have been keeping their patients in bed for only 6 or 10 days rather than 28 or 30 days.

The control of epidermophytosis is of very great importance in patients with the idiopathic type of thrombophlebitis. Some believe that there is a very close causal relationship between fungus infection and thrombophlebitis of the lower extremities, either allergic or by direct invasion of the vein by the infectious agent. Also, the fungus produces cracks in the skin which facilitate entry of secondary invaders. In many patients who have had thrombophlebitis repeatedly, recurrences are apparently prevented by the simple expedient of keeping the dermatophytosis under control.

There is one point, the importance of which I cannot emphasize too strongly, namely, that of refraining from making physical examinations of the chest, in which patients are instructed to take deep breaths for the purpose of determining whether or not an infarction of the lungs has taken place, or where the infarct is located. Deep breathing increases the negative pressure in the chest, thereby increasing the speed of blood flow from the extremities, which may break off the loose tails of the thrombi. If a person was operated upon 10 days previously, or if he has an acute phlebitis and suddenly develops a stabbing pain in the chest and coughs up some blood, it is quite probable that he has developed a pulmonary embolus. It is of minor importance to learn exactly where the infarct is. That is purely an academic question. There have been several deaths following shortly upon such examinations. So far this

fatal pulmonary embolus; therefore, all thrombophlebit must be regarded as serious and potentially fatal if steps a not taken to prevent the formation of emboli.

Let us consider briefly the several therapeutic measur which have long been studied, although in the case of some them considerable doubt still prevails regarding the best pr cedure. I believe there is a fairly universal agreement toda that, in the case of a patient with thrombophlebitis of the low extremity, with edema, elevation of the extremity is helpf in reducing the edema to a minimum. To keep the affecte extremity in a dependent position or at the level of the body of no therapeutic value and may actually be harmful.

Whether heat or cold should be applied to such patients h long been debated. The consensus at present seems to fav heat, if properly applied. I am not sure that we know how apply it properly. The technic described by Barker is n most acceptable. The affected extremity is carefully cover with a thin layer of petrolatum or similar substance to preve maceration of the skin, and a moist, hot pack is applied. Th may be in the form of turkish towels dipped in hot wat wrung out and laid loosely around the extremity, which then covered with a rubber blanket and surrounded by h water bags. The hot pack is kept on for 20 out of 24 hou allowing 4 hours for aeration and drying of the skin In sev cases with marked edema, both lumbosacral sympath block and hot packs may be used simultaneously. The ap cation of hot packs to an extremity immediately after lum sacral block seems to prolong the vasodilating effect of block, reducing vascular spasm and permitting more drainage.

The matter of activity versus rest has long been debat and it is still unsettled. There are some who believe that should wrap a bandage tightly around an affected leg and struct the patient to walk 40 to 60 blocks a day, if there

dangerous procedure has received only brief mention in the literature. Sliding an X-ray cassette under the patient's chest is a much safer way of locating an infarct.

A patient should also be advised against violent coughing and straining at stool, and it is up to the doctor to see that the patient does not indulge in either. There have been a number of patients with thrombophlebitis who have died during defecation. I knew one patient who died under these circumstances a month after she was discharged from the hospital, at a time when the thrombophlebitis appeared to have subsided completely.

Venous ligation as an aid in treating thrombophlebitis has had a troubled history. It appears as though its exponents have been chasing the rainbow's end from the lower saphenous vein all the way up to the superior vena cava. One of the shortcomings of treatment by ligation is that emboli may result from thrombi forming at the site of any ligation. Thrombophlebitis and varicosities also recur sometimes after ligation of the affected vein. I have a patient in the hospital now who never did have an embolus from the original thrombophlebitis, but promptly after a bilateral femoral ligation began to have emboli and continued to have them until treated with anticoagulants. Edema may also sometimes occur following ligation. It is maintained by the exponents of ligation of the inferior vena cava that following this procedure there is less edema than is seen after femoral ligation, but on reading the reports of a few years ago, one sees that some enthusiasts then maintained that there was no edema following femoral ligations. I believe there are specific indications for ligation, but this procedure should not be used indiscriminately. It is indicated if there is a lesion in a lower extremity which gives rise to recurring emboli. Ligation is a much safer procedure now that anticoagulant therapy is available, and anticoagulant therapy should always be used following venous ligation. Varicose veins, of course, constitute the major field for ligation, and no

dangerous procedure has received only brief mention in the literature Sliding an X ray cassette under the patient s chest is a much safer way of locating an infarct

A patient should also be advised against violent coughing and straining at stool, and it is up to the doctor to see that the patient does not indulge in either There have been a number of patients with thrombophlebitis who have died during defecation I knew one patient who died under these circumstances a month after she was discharged from the hospital, at a time when the thrombophlebitis appeared to have subsided completely

Venous ligation as an aid in treating thrombophlebitis has had a troubled history It appears as though its exponents have been chasing the rainbow's end from the lower saphenous vein all the way up to the superior vena cava One of the shortcomings of treatment by ligation is that emboli may result from thrombi forming at the site of any ligation Thrombophlebitis and varicosities also recur sometimes after ligation of the affected vein I have a patient in the hospital now who never did have an embolus from the original thrombophlebitis, but promptly after a bilateral femoral ligation began to have emboli and continued to have them until treated with anticoagulants Edema may also sometimes occur following ligation It is maintained by the exponents of ligation of the inferior vena cava that following this procedure there is less edema than is seen after femoral ligation, but on reading the reports of a few years ago one sees that some enthusiasts then maintained that there was no edema following femoral ligations I believe there are specific indications for ligation, but this procedure should not be used indiscriminately It is indicated if there is a lesion in a lower extremity which gives rise to recurring emboli Ligation is a much safer procedure now that anticoagulant therapy is available, and anticoagulant therapy should always be used following venous ligation Varicose veins, of course, constitute the major field for ligation, and no

one can dispute the importance of the operative procedure in these cases

Now we come to another subject of considerable controversy namely anticoagulant therapy Heparin was the first of the clinically effective anticoagulant agents We have followed its use with great interest since it became available in this country for the treatment of thrombophlebitis It prolongs the coagulation time Statistics clearly show that it markedly reduces the number of pulmonary emboli and the number of deaths It is administered as most of you know, either by continuous intravenous infusion so as to keep the coagulation time preferably between 20 and 45 minutes or by repeated intravenous injections of 75 mg every 3 or 4 hours This method produces marked fluctuations in the coagulation time as high as 100 minutes shortly after the injection with a return to normal before the next injection Dr Loewe has been developing a menstruum which releases heparin slowly The present menstruum for an intramuscular injection cannot be considered entirely satisfactory its injection is extremely painful to the patient it is difficult to control and it produces nausea in some patients However I think it is a move in the right direction and the subject should be pursued further There are many disadvantages in the use of heparin It is an expensive procedure So far it can be administered only by injection and the danger of hemorrhage from improper use is well known It requires close supervision by the house staff both day and night for the duration of its administration in order to check the blood coagulation time although with the intermittent method the number of checks of coagulation *time is reduced markedly*

Dicumarol has now become more popular It is inexpensive It can be given by oral administration Dicumarol interferes with the production of prothrombin and it affects the coagulation time There has been some question about the effect of dicumarol on the coagulation time and unless the test is prop

erly made, one may fail to detect a prolongation of the coagulation time In this connection a word should be said about the Lee White glass tube method Some important work has recently been undertaken in a number of institutions to study the types of tubes other than glass, because it has long been recognized by those of us working in the field of peripheral vascular diseases that the glass tube Lee White method does not even remotely represent coagulation time as it occurs in the blood vessels I should like to quote some hitherto unpublished figures from Dr Kadish of the Mayo Clinic Using the Lee White method he found the coagulation time to be 6 to 7 minutes with the glass tube, 13 to 14 and even up to 19 minutes with the lucite tube, and considerably higher values with the collodion or paraffin tube With the lucite tube the normal value of 13 to 19 minutes is found shortened to 6 to 8 minutes in those patients with thrombophlebitis and prolonged to 30 to 40 minutes or more in a patient taking dicumarol Even with the glass tube, if the test is carefully performed, it can be shown that dicumarol prolongs the coagulation time, but the use of the lucite tube provides a much more sensitive method for demonstrating this change In our laboratory, however, the results with the lucite and other tubes have been too unpredictable to be used as a guide to dicumarol dosage

Dicumarol therapy also has several disadvantages It requires daily prothrombin tests and the laboratory must be prepared to do them It is difficult to get laboratories to do the test accurately As with heparin, there is the risk of hemorrhage if the patient is not watched carefully There are several gaps in our knowledge of the action of dicumarol Work on intravascular clotting in animals is not sufficient, so our knowledge of the action of dicumarol has to advance largely by cautious experiments on man

There are some very striking figures in studies on the value of dicumarol therapy One might mention those of Barker and his group at the Mayo Clinic, in which they compared the

results in 897 patients with thrombophlebitis treated without anticoagulant agents before emboli developed, with the results in 138 similar patients treated with dicumarol. An incidence of 10.6 per cent of subsequent thrombophlebitis or pulmonary embolism was reduced to 2.9 per cent in the group with dicumarol; also, an incidence of 5.7 per cent of fatal pulmonary embolism was reduced to 0 per cent in those treated with dicumarol. They also made another type of analysis. They compared the results in 678 patients who had suffered one or more non-fatal emboli and did not receive anticoagulant therapy, with the results in 180 similar patients treated with dicumarol. An incidence of 43.8 per cent of subsequent thrombosis or embolus was reduced to 1.1 per cent in those treated with dicumarol; also, an incidence of 18.3 per cent of fatal pulmonary embolus was reduced to 0.6 per cent in those treated with dicumarol. It is noteworthy that substantially similar results in very large groups of patients have been reported by Jorpes and his collaborators from the Karolinska Institut in Stockholm, where they used heparin in some patients and dicumarol in others.

Dr. Andrus: As Dr. Wright has pointed out, the therapy of thrombophlebitis is complicated and none of the various methods of treatment which have been used in the past have been entirely satisfactory, but certainly a great advance has been made with the use of anticoagulant therapy I think that perhaps the internists and surgeons, while they see the problem from a common point of view in many ways, look upon certain aspects of it somewhat differently. I will ask Dr. Glenn to discuss this problem from the surgical point of view.

Dr. Frank Glenn: To the surgeon, pulmonary embolism is always a matter of grave concern, and the surgeon's attack on it must begin with the preoperative preparation of the patient and the care of the patient during the operation.

It seems to me that the care which has been exercised in the operating room in the past few years to maintain the patient's

blood pressure at a proper level has been of great importance in reducing the incidence of postoperative thrombophlebitis The fall of the blood pressure to a low level and the associated shock certainly favor coagulation of blood especially in the vessels of the lower extremity The care of the patient after operation is equally important Having the patient do exercises while in bed and employing early ambulation help to reduce the incidence of thrombophlebitis and emboli especially those fatal emboli which arise from the lower extremity Statistics from various laboratories of pathology show that the majority of these fatal emboli from the lower extremity arise from the deep femoral circulation When conservative measures fail to prevent the appearance of emboli or thrombophlebitis the surgeon naturally takes more active steps

There has been a great deal said about ligation In our clinic here we do not follow in the footsteps of some of those farther up the coast who even do prophylactic ligation Nevertheless when one is confronted with what appears to be a thrombophlebitis with embolism interruption of the deep circulation is certainly indicated It should be undertaken immediately Where one may limit treatment to the use of anticoagulant therapy alone is a question that has certainly not been settled especially in the surgical cases

In tracing the history of ligation one finds that the first approach involved ligation of the superficial circulation Division of the deep femoral circulation was not attempted until later For the majority of patients the division of the deep femoral vessels is probably the procedure of choice I certainly believe that following ligation of these vessels the incidence of emboli has been reduced Along with the interruptions of the deep femoral circulation anticoagulant therapy as already outlined is certainly indicated Some object to operative procedures because of the edema and disability which may result Generally speaking we have found that division of the deep femoral circulation is not followed by as much edema as one is

led to believe Usually the higher the interruption of the venous return the better is the collateral circulation which is thereafter established If a patient has been ill for a long time, or has had some surgical procedure involving one extremity and thrombophlebitis has developed then the choice rests between a bilateral ligation of the femoral and the common iliac vessels In patients with pelvic involvement ligation of the inferior vena cava is indicated This is an heroic procedure and is occasionally fatal but I believe it can be utilized to good advantage if combined with anticoagulant therapy

Dr Andrus The topic today is the treatment of thrombophlebitis but I am sure that all of those interested in the subject agree that the most important aim is the prevention of thrombophlebitis Unfortunately, our understanding of the factors which produce it is very meager However I think that we do know of certain measures which tend to diminish the incidence of thrombophlebitis such as the avoidance of infection the prevention of stasis in the veins of the legs resulting from the use of tight dressings from distention of the abdomen or from the low blood pressure of shock The use of deep breathing exercises prophylactically after operation has been widely employed as well as the use of routine postoperative exercises with the patient in bed until early ambulation is feasible Deep breathing is used to prevent venous stasis It is certainly to be carefully avoided if thrombophlebitis is present or even suspected No methods of prevention are universally successful It is to be hoped that continued investigation will give us greater understanding of this complicated group of diseases and will reveal more effective means of prevention and better therapeutic agents

Dr Wright will you make a few remarks on the diagnosis of thrombophlebitis? How do you demonstrate its presence?

Dr Wright I wish to say first that I agree with Dr Andrus that if we keep these individuals active get them out of bed very early move their legs have them exercise in bed and take

blood pressure at a proper level has been of great importance in reducing the incidence of postoperative thrombophlebitis The fall of the blood pressure to a low level and the associated shock certainly favor coagulation of blood especially in the vessels of the lower extremity The care of the patient after operation is equally important Having the patient do exercises while in bed and employing early ambulation help to reduce the incidence of thrombophlebitis and emboli, especially those fatal emboli which arise from the lower extremity Statistics from various laboratories of pathology show that the majority of these fatal emboli from the lower extremity arise from the deep femoral circulation When conservative measures fail to prevent the appearance of emboli or thrombophlebitis the surgeon naturally takes more active steps

There has been a great deal said about ligation In our clinic here we do not follow in the footsteps of some of those farther up the coast who even do prophylactic ligation Nevertheless, when one is confronted with what appears to be a thrombophlebitis with embolism, interruption of the deep circulation is certainly indicated It should be undertaken immediately Where one may limit treatment to the use of anticoagulant therapy alone is a question that has certainly not been settled, especially in the surgical cases

In tracing the history of ligation, one finds that the first approach involved ligation of the superficial circulation Division of the deep femoral circulation was not attempted until later For the majority of patients the division of the deep femoral vessels is probably the procedure of choice I certainly believe that, following ligation of these vessels the incidence of emboli has been reduced Along with the interruptions of the deep femoral circulation, anticoagulant therapy, as already outlined, is certainly indicated Some object to operative procedures because of the edema and disability which may result Generally speaking, we have found that division of the deep femoral circulation is not followed by as much edema as one is

led to believe Usually the higher the interruption of the venous return the better is the collateral circulation which is thereafter established If a patient has been ill for a long time or has had some surgical procedure involving one extremity and thrombophlebitis has developed then the choice rests between a bilateral ligation of the femoral and the common iliac vessels In patients with pelvic involvement ligation of the inferior vena cava is indicated This is an heroic procedure and is occasionally fatal but I believe it can be utilized to good advantage if combined with anticoagulant therapy

Dr Andrus The topic today is the treatment of thrombophlebitis but I am sure that all of those interested in the subject agree that the most important aim is the prevention of thrombophlebitis Unfortunately our understanding of the factors which produce it is very meager However I think that we do know of certain measures which tend to diminish the incidence of thrombophlebitis such as the avoidance of infection the prevention of stasis in the veins of the legs resulting from the use of tight dressings from distention of the abdomen or from the low blood pressure of shock The use of deep breathing exercises prophylactically after operation has been widely employed as well as the use of routine postoperative exercises with the patient in bed until early ambulation is feasible Deep breathing is used to prevent venous stasis It is certainly to be carefully avoided if thrombophlebitis is present or even suspected No methods of prevention are universally successful It is to be hoped that continued investigation will give us greater understanding of this complicated group of diseases and will reveal more effective means of prevention and better therapeutic agents

Dr Wright will you make a few remarks on the diagnosis of thrombophlebitis? How do you demonstrate its presence?

Dr Wright I wish to say first that I agree with Dr Andrus that if we keep these individuals active get them out of bed very early move their legs have them exercise in bed and take

are in effect the same as reducing the concentrations of prothrombin), it has been found, for example, that by the time the prothrombin content has been reduced to as low as 30 per cent of the normal, clotting has been only moderately impaired as shown by the fact that the 'prothrombin time' has only risen from about 12 to 18 seconds, or a rise of only about 50 per cent Beyond a given point, however, even slight further reductions in the prothrombin content (prothrombin activity) greatly influence blood clotting, and produce large increases in the prothrombin time, for example, a reduction of the prothrombin activity from 30 to 10 per cent of the normal delays clotting so much that it raises the prothrombin time from 18 to 38 seconds, that is, a rise of about 100 per cent The point of this is to emphasize the need for bearing in mind the difference between the terms 'prothrombin activity' and "prothrombin time' One must also remember that after a conspicuous rise in prothrombin time has taken place with dicumarol therapy, the patient must be watched carefully for small additional doses of the drug by causing further small reductions in the prothrombin content, may produce abrupt rises in the prothrombin time, blood clotting being so markedly impaired as to give rise to spontaneous hemorrhages

In the actual carrying out of the test for the prothrombin time in the laboratory, there appear to be so many variables that it is necessary to have a control subject tested at the same time, as a means of insuring the accuracy of the test It might be well for the physician to consult with the laboratory which performs the prothrombin test for him in order to be sure of the precise meaning of the figures which are reported to him, since the results obtained by different laboratories are somewhat different depending on the conditions of the test

I should like to ask Dr Wright what percentage of bed patients who develop a pulmonary embolus give evidence of thrombophlebitis prior to the embolus

Dr Wright I do not know of any adequate figures on that

point Perhaps some of the surgical staff can answer the ques tion more specifically

Dr Andrus After an embolism occurs you can nearly al ways determine where it came from, but I know of no figures on the percentage of patients in whom the diagnosis of throm bophlebitis is made or is possible before emboli have occurred

Dr Harold E B Pardee In relation to Dr Gold s question, I think it is only in a small percentage of patients that one recognizes signs of thrombophelebitis prior to the embolic phenomena

Dr Gold I agree with that I have seen many cases of pul-monary embolus in non surgical patients but I can recall only two instances in which signs of phlebitis presented themselves prior to the embolus to suggest the possibility of embolus It may be that the signs of thrombophlebitis are often not very conspicuous and we do not look carefully enough in medical patients confined to bed

Dr Andrus I would certainly claim no special ability for the surgical service, for I know there are many patients in whom we recognize the thrombophlebitis only after the em-bolus but there are certainly a great many in which we recog nize thrombophlebitis beforehand I would guess that we rec ognize the phlebitis in about half of the patients before they have an embolus

Dr Wright Do you not think that our house physicians should be trained to make daily observations postoperatively on the legs of all patients? I am sure that many more of these cases would be recognized if that were a standard procedure on all surgical services

Dr Pardee How long do you believe anticoagulant therapy should be continued, and what criteria would you use for stop-ping it?

Dr Wright It depends on the type of case We like to keep the individual who has had a simple thrombophlebitis of short duration on anticoagulant therapy for 3 to 4 weeks I have re-

in a while an article appears recommending 1 000 mg of dicumarol as the first dose Such dosage is extremely dangerous One may give 300 mg as the first dose relatively safely and 300 mg on the second day then tapering off gradually to 200 mg and 100 mg daily If that dosage system is accompanied by a careful daily check of the prothrombin time I do not think one will get into trouble very frequently, but one may anticipate some minor hemorrhages

Before we close this discussion I think I should say a word about the care of the patient after he recovers from the acute thrombophlebitis Such care is one of the most important but also one of the most neglected phases of the management of this disease We must remember that thrombophlebitis can be arrested but it should never be regarded as cured Most of these patients have pains when they stand a long time and when the barometer changes They worry about these pains and many of them become psychoneurotic because they never know whether the pain presages another attack of phlebitis The neglect of proper prophylactic care increases the tendency to edema ulcers and varicose veins We can prevent these unfortunate sequelae by several means It was found that a group of patients wearing knee length well made individually fitted elastic stockings for the first year after their thrombophlebitis had at the end of five years far less edema far fewer pains and far fewer ulcers of the legs than those patients who went without stockings I think that the use of such stockings is very important It is essential to instruct the patient on how to prevent dermatophytosis It is also most necessary to explain to the patient that pains in the legs do not always mean a recurrence of the thrombophlebitis Fear of a recurrence may be one of the most serious disabilities We have seen patients who five years after the attack are fearful of moving about or unnecessarily restrict their activities because they fear that when they have a pain in their leg they are on their way to a recurrence This reaction is understandable in people who have passed

through two or three attacks. We have formulated some arbitrary rules which have proved helpful to these patients. If the pain lasts less than an hour they should ignore it, for most of these pains last less than 15 minutes. If it lasts 1 to 3 hours, they should lie down and elevate the feet or get into a tub of cool water, which frequently gives relief. If it lasts more than 3 hours, they should call their physician. Most of them will say, "Well, now that I know I don't have to worry about pain that lasts less than an hour, I go ahead and do what I want to do and have stopped worrying about it." Some pains may recur for several years after an acute attack, and the patient's failure to understand this may result in much needless physical and psychoneurotic invalidism.

SUMMARY

Dr. Lawrence W. Hanlon: Some of the problems of treatment of thrombophlebitis were explored this afternoon. There are many varieties of thrombophlebitis differing in their causes, clinical aspects, and pathologic changes. The regimen of treatment should be adjusted to the special requirements of the particular patient. The differentiation between phlebothrombosis and thrombophlebitis has limited value, since, after a time, the thrombi in the two become pathologically indistinguishable. While thrombophlebitis often makes its appearance with characteristic signs and symptoms, such as pain, tenderness, swelling, fever, and elevated sedimentation time, in many of these patients the onset is silent and the first indication of the disease is a pulmonary embolus. Emphasis was placed on the desirability of making routine systematic examinations of the legs in surgical and non-surgical patients confined to bed, as a means of uncovering cases of thrombophlebitis sufficiently early to make it possible to prevent pulmonary complications.

The discussion covered measures that are useful in the prevention of thrombophlebitis, such as care against traumatiza-

tion of vessels, prevention of infection, control of epidermophytosis, free movement in bed, early ambulation deep respiratory exercises and the avoidance of the latter in thrombophlebitis to prevent pulmonary embolism Attention was called to the highly controversial nature of the measures used in the treatment of thrombophlebitis the application of heat and cold, the use of leeches prolonged rest free exercise early ambulation dependent and elevated position of the extremity lumbosacral sympathetic block, prophylactic venous ligation and the use of anticoagulant agents It was indicated that the consensus favors hot, moist packs to the affected extremity the elevated position of the limb to control swelling and a middle course in relation to rest and activity, the patient being allowed up and about after a short period of rest even though the disease is not fully checked, provided anticoagulant therapy is employed There are those who recommend prophylactic ligation of the veins in thrombophlebitis of the lower extremity in order to prevent embolism although others prefer a more conservative course, ligating only after there is proof that the vein is a source of recurrent embolization The choice of site for ligation depends on the location of the phlebitis

The use of the anticoagulant agents heparin and dicumarol appears to be an advance of the first importance in the treatment of thrombophlebitis Figures were cited showing most extraordinary results following their use for example second thrombosis or embolus was reduced from an incidence of nearly 50 per cent to about 1 per cent cases of fatal pulmonary embolus with an incidence of nearly 6 per cent completely vanished The discussion embraced the details of application dosage mode of action, dangers and methods of control of anticoagulant therapy

Treatment of Alcoholism

Dr Harold G Wolff We will consider today the problem of alcoholism It is difficult to determine the extent of this malady It has been conservatively estimated by Kolb, of the United States Public Health Service, that perhaps 2,500,000 people in the United States are addicted to alcohol to a degree that in some way interferes with their effectiveness and the fulfillment of their potential It is thought by Kolb also, that approximately 200,000 of these are seriously sick—and the problem of helping them has not been solved Dr. Rennie will open the discussion

Dr Thomas A C Rennie From 10 to 25 per cent of admissions to state hospitals are for conditions associated with alcoholism In addition alcohol runs very high as one of the major causes of psychoses

There is a growing awareness, fortunately, of the fact that alcoholism is a disease, not a weakness of character, and that the alcoholic represents a human being who is escaping from intolerable stresses or strains Hence, there is a very large emphasis now on psychotherapy in the treatment of these individuals. Satisfactory treatment is not yet the rule, however From a manuscript just released, representing a year's study by the Committee on Public Health Relations of the New York Academy of Medicine, come the following rather interesting facts which point to the dearth of facilities for the treatment of the alcoholic The figures are based on 1 609 replies to a questionnaire which was sent to several thousand practicing physicians in New York. Chronic alcoholics are treated by

about 75 per cent of the psychiatrists who replied by about 50 per cent of the general practitioners and by 46 per cent of the internists They all said they treated some alcoholics however only 0 4 per cent of those replying said they treated more than 10 per cent of their total practice for problems of alcohol or in other words made any sort of specialty of that problem in treatment The percentage treating the acute alcoholic was about equal for the psychiatrist the internist and the general practitioner, with a slightly heavier weighting for the internist

The methods used in treatment ran a strange gamut of performances The largest number of physicians stated that they used psychotherapy A number of them who were questioned as to what they meant by psychotherapy had great difficulty in explaining what it is The next most common form of treatment was hospitalization (when it was possible to secure a hospital bed) Other forms of treatment relied heavily upon nutritional aspects massive doses of vitamins or sedatives in one form or another Some physicians not psychiatrists mentioned that they used group psychotherapy Others stated that they used electric shock therapy a few that they used conditioned reflex therapy although few were able to describe what conditioned reflex therapy is Among the psychiatrists about 40 per cent referred patients to Alcoholics Anonymous and about 23 per cent referred patients to various social agencies in the community

It is difficult to get an alcoholic patient into a hospital in this area and this is a problem throughout the country as well According to the answers to the questionnaire the largest number of patients goes either to Bellevue or Kings County hospitals both of which have psychiatric divisions and accept alcoholic patients the next largest number goes to the Doctors Hospital the next to the Towns Hospital and so on down

Since 1945 all the municipal hospitals in the City of New York have been accepting alcoholic patients and putting them

on the medical services only a few have special wings for the treatment of alcoholics

The Knickerbocker Hospital about two years ago set aside 15 beds for the treatment of alcoholics referred by and in contact with Alcoholics Anonymous In the last five years from 8 000 to 12 000 patients per year entered Bellevue and New York municipal hospitals for alcoholism their average stay being less than 72 hours Often they come in at night and go out in the morning It is apparent that hospital facilities for the treatment of this great problem are inadequate

Since psychologic factors in alcoholism are now being stressed the psychiatrist s definition and classification of the alcoholic should be of interest as well as of importance in the treatment of the alcoholic. What is a chronic alcoholic? He may be defined as an individual who is unable to do without alcohol who is completely and daily dependent upon alcohol for his comfort and who is apt to take his first drink early in the morning of each day He is a person who cannot function harmoniously or contentedly without alcohol

We recognize two large groups of chronic alcoholics the spree drinker and the steady drinker The spree drinker presents a special kind of psychologic problem He is a man who may not drink for months at a time and then goes off on a spree or bender This may last one day to a week or two during which he drinks extremely heavily often locking himself in his room refusing to see people He comes out of the spree a few days or a week or so later and has no desire for alcohol again for perhaps weeks or months or even years

The steady drinkers however are persons who have to have alcohol every day and these are usually divided in an attempt at classification into 4 major categories One is that of the individual who has intolerable problems in his life He knows what they are but he cannot meet them with comfort and he finds solace in alcohol The second is that of the so-called psychoneurotic individual whose difficulties problems and con

flicts lie largely within himself, often unknown to him and who finds that alcohol relieves the intolerable conflict. The third category is that of the person whose use of alcohol is a symptom of a more fundamental underlying psychiatric disorder Thus, we see patients in depression turning to alcohol manics turning to alcohol to celebrate Schizophrenic patients and the feeble minded are also easy prey to alcohol The fourth category is that of individuals in whom the personality component is not immediately striking, who just regularly and persistently take alcohol because they like the taste and effect of it.

The treatment of the psychologic factors which lead to acute and chronic alcoholism, of course, cannot be considered here in detail There are, however, clinical problems arising out of these conditions which demand immediate treatment Let us consider the management of acute alcoholism I shall not burden you with the details of the picture of acute alcoholism for you all have seen it It is usually self limiting, harmless and apt to be slept off quite satisfactorily, however, coma can intervene in an acute alcoholic spree and may require intensive treatment

Great reliance is now being placed upon two major aspects of treatment These stem from the more recent advances in the knowledge of the metabolism of alcohol It is oxidized in the body rather slowly, about 10 cc per hour, this is best accomplished in the presence of insulin and glucose which facilitate its oxidation in the liver Vitamin B fractions, particularly thiamine and nicotinic acid, are also of value in this respect

Almost all treatment for acute alcoholism, delirium tremens, and other acute alcoholic conditions include the combined use of glucose and insulin Usually 1,000 to 2,000 cc of a 5 to 10 per cent solution of glucose is given intravenously, together with 20 or 25 units of insulin, given subcutaneously To this there is usually added, also by the parenteral route 50 to 100 mg of thiamine chloride and 100 mg of nicotinic acid At Belleuve Hospital 100 mg of ascorbic acid, as well as 5 mg

of riboflavin by mouth per day is given In that institution they also add 100 mg of pyridoxine to the regimen in the belief that it may reduce the vomiting which so commonly is part of the picture of acute alcoholism Alcoholics require a high caloric diet with large amounts of protein as well as of carbohydrate It seems evident therefore that adequate nutrition with vitamin supplementation constitutes the backbone of the treatment as well as of the prevention of the serious sequelae of alcoholism

There are however additional important aspects in the care of the comatose alcoholic patient He should be kept warm turned frequently to prevent pneumonia and given stimulants if necessary If the respiration is depressed seriously a carbon dioxide and oxygen mixture may be used Large amounts of fluids with electrolytes are required because alcoholics usually lose a considerable amount of fluid and sodium chloride in vomitus and diarrhea Every patient of course deserves a meticulous physical examination so that fractures brain injuries diabetes and uremia are not overlooked The only real dangers usually are those of circulatory collapse or pneumonia

Delirium tremens presents different problems for treatment The delirious react with great fear and panic have terrifying visual hallucinations which are usually of small animals and bugs There is disorientation the patient does not know where he is and cannot grasp the significance of the environment about him There is a characteristic tremor which gives rise to the name of the disorder Delirium tremens is usually a self limiting disease running anywhere from 1 to 5 or 6 days with almost invariable recovery Hospitalization is preferable for the management of these patients

Good nursing care is important The patients are frightened and need constant reassurance They find it difficult to orient visibly and should be kept either in a room brightly lighted or in one completely dark Because they are disoriented and

confused, they frequently mistake windows for doors and it is therefore, necessary to guard against serious accidents or inadvertant suicides

Hydrotherapy is used commonly in the acute case of delirium tremens The rest of the treatment is largely supportive Treatment includes the use of vitamins sedatives and the insulin and glucose combination already mentioned The most commonly used sedative is paraldehyde 10 to 20 cc by mouth or in smaller doses intramuscularly if the patient is unable to take it orally Chloral hydrate is also used in 0 5 to 1 Gm doses and more rarely the barbiturates particularly sodium amytal in 0 25 or 0 3 Gm doses Some physicians do not use barbiturates in alcoholics because they fear the development of dependence

These patients also need large amounts of fluid and sodium chloride Routine care also includes a high caloric diet preferably fluid (often delirious patients are not able to tolerate solids because of persistent gastritis) and large amounts of carbohydrate and protein In about 5 days the patient usually recovers without sequelae One danger in delirium tremens is that of circulatory collapse Subdigitalization is sometimes carried out if there are signs of cardiac distress so that the patient can be digitalized more rapidly if it should become necessary

There is a group of disturbances resulting from or associated with the long continued use of alcohol which I have time only to enumerate but of which we must be aware acute alcoholic excitement pathologic alcoholism with epileptoid manifestations acute or chronic hallucinosis alcoholic deterioration jealousy and paranoid reactions Korsakoff s psychosis and the Wernicke syndrome Many of these are primarily vitamin deficiency disorders only secondarily due to the use of alcohol These complications develop because of poor appetite deficient food intake and the vitamin inadequacy that almost invariably accompanies it Their treatment involves restoration of vitamins by massive doses either orally or hypo-

dermically over a long period of time Some of these disorders do not clear up rapidly even though the vitamin deficiency is treated

Finally we come to the problem of the chronic alcoholic the psychologic types of which I have already defined The chronic alcoholics are best treated in a hospital although very few of them are willing to accept that formulation Hospitalization removes the alcoholic from all sources of alcohol In the hospital he is separated from an environment which is stressful Hospitalization offers a neutral environment in which the nursing staff as well as the physicians are understanding of his problems The psychiatrist has the opportunity to observe his day by day reactions and his responses to other patients to analyze his anxiety reactions as they occur and to proceed much more rapidly with the psychotherapeutic exploration For these reasons hospitalization is desirable and for a fairly protracted period a minimum of 3 and preferably 6 months or longer

In New York State it is not possible to commit alcoholics Revision of the laws of the State to make this possible should be given careful consideration because one of the great difficulties with the complete treatment of chronic alcoholics is that usually 4 to 6 weeks after they have stopped drinking they attain a state of mild euphoria and think their problems are solved and they no longer need to go on with therapy If they demand it they must be released from the hospital Alcoholics can petition for a voluntary commitment In such a case hospitalization can be ordered by a judge and the patient kept in a hospital until cured even though the patient may wish to leave earlier

The first problem of course is to get the alcoholic to stop drinking At Payne Whitney we withdraw alcohol immediately We feel that there is no valid psychologic reason for a tapering-off procedure Removal of alcohol requires strong reassurance suggestive measures attention to dietary needs

Problems of Alcohol, a national organization in New York devoted to the aspects of research into the causes and prevention of alcoholism Another is the National Committee for Education on Alcoholism, also in New York, and the third the National Committee of Alcohol Hygiene is located in Baltimore These organizations provide more specific help in the management and understanding of this problem

Dr Wolff Dr Rennie, in referring to the management of the acute alcoholic you spoke about the use of stimulants What did you mean specifically?

Dr Rennie The one most commonly used is caffeine and sodium benzoate 0 5 to 1 Gm Another fairly common one is amphetamine sulfate, 5 and 10 mg

Dr Cary Eggleston Circulatory rather than cardiac stimulants?

Dr Rennie Yes

Dr Wolff Is anyone convinced that giving vitamins to a person in the acutely alcoholic state could be effective in the short time that the individual remains in that state? I take it that it would be a matter of 12 or 14 hours at the most

Dr Harry Gold There does not seem to be very much doubt that the actions of the vitamins may appear fairly quickly A bird that is unable to fly because of vitamin B_1 deficiency may be able to fly off within a few hours after a massive dose of vitamin B_1 A person with scurvy may after a massive dose of vitamin C show unequivocal improvement within 24 hours This also, applies to the case of defective dark adaptation, after a massive dose of vitamin A

If these patients are really suffering from a vitamin deficiency and receive adequate doses, considerable improvement might take place in the course of a few hours after administration

Dr McKeen Cattell Dr Wolff although I think there is a certain amount of logic in the use of insulin and glucose I would like to point out that too much should not be expected

from them I do not remember the exact figures now, but approximately half of the total metabolism may result from the burning of alcohol It is apparent that this percentage cannot be increased very much without burning up the individual I think the actual increase in the elimination of alcohol by that procedure cannot be very important

Dr Wolff It could perhaps have some other rôle than that in total elimination Could it have a specific effect in tissue?

Dr Cattell That might well be as a matter of fact it is known that life may be protected by such treatment The procedure possibly may be worth while in the treatment and there is some evidence that the addition of glucose may improve central nervous function but I was thinking of the usual explanation that is given As far as promoting elimination is concerned I believe that that cannot be accomplished to any important degree

Dr Wolff I would like to ask about subdigitalization in patients with delirium tremens Dr Gold would you suppose, if a person were in danger of circulatory collapse as the result of this disorder that it would make much difference whether he were getting subdigitalization doses or full doses or none at all?

Dr Gold Unless there is fairly clear evidence of heart failure I believe that digitalis would have no influence at all

Dr Rennie The only death I have ever seen in a delirium tremens was due to cardiac failure

Dr Gold And not peripheral circulatory collapse?

Dr Rennie No heart failure

Dr Gold Of course since there are about 13 000 000 cardiac patients in the United States and 2 500 000 people with alcoholic troubles it would not be strange if coincidence produced a patient with both conditions from time to time I should think in the absence of heart disease the problems of the heart in delirium tremens would not be those requiring digitalis

Dr. Wolff: Would you suppose that alcohol would harm a heart that was not in failure or beginning to fail?

Dr. Gold: I doubt very much that it would in the range of concentrations in humans.

Dr. Wolff: If it did, would you suppose digitalis would make any difference?

Dr. Gold: I would doubt it.

Dr. Wolff: Dr. Rennie, we see, from time to time, individuals who have been addicted to one form of a sedative or who take sedatives for convulsions, who have fits precipitated by the sudden withdrawal of such a medicament. Apparently there is danger of fits in the alcoholic who suddenly has his alcohol withheld (Dunning, *International Clinic III*, vol. 3, 1940). When you say that alcohol should be *completely* and suddenly withdrawn in chronic alcoholics, do you consider such a possibility? Is hydrotherapy, and I assume you mean submersion in a tub for hours, sufficient, or might the alcoholic, in addition, receive a bromide, a barbiturate, or some agent other than alcohol, or would you withdraw all medicaments during this precarious period?

Dr. Rennie: I would not withdraw all medicaments. Routinely, in a delirium tremens patient, when I remove alcohol, I replace it with a sedative, preferably paraldehyde. Most alcoholics prefer it, and it also seems to be about the most effective one. No, I would not remove alcohol and leave that person with no support at all. He is much too tremulous, anxious, and frightened. He clearly needs sedation as well as prolonged baths. This holds for the management of the chronic, the acute alcoholic, as well as the patient with delirium tremens.

May I say something about the convulsive manifestation?

Dr. Wolff: Please do.

Dr. Rennie: There is a very rare condition associated with alcohol, but more with the ingestion of it and not with the cessation of it, and that is the condition which I designated as pathologic with epileptoid manifestations. There are certain

individuals probably epileptoid who may not have convul sive seizures without alcohol but who show them after the long continued use of it I have only once observed the production of a convulsion as the result of the withdrawal of alcohol

Dr Wolff You referred in your discussion of the manage ment of delirium tremens to the use of sodium chloride and large amounts of fluid Is there not the impression—and per haps I am wrong—that some of these people have wet brains?

Dr Rennie Dr Wolff is needling me because I wrote a manuscript recently in which I recommended hypertonic glu cose for the edema of the brain. Dr Wolff you can answer that question better than I can

Dr Wolff Although postmortem edema in patients with delirium tremens has been considered to be present by Nazum and Le Count (*J A M A* 67 1822 1916) I am personally not convinced that it makes much difference whether one gives more or less than the usual amount of fluid or salt. Perhaps some of these people are pretty dry after hours without fluid or food and therefore are entitled to fluid for reasons of their dehydration

Dr Rennie Most of them are usually badly dehydrated

Dr Gold What is the fact in relation to hypertonic glucose solution? Does it seem to make them better or is it one of those practices continued by the momentum of tradition?

Dr Rennie Dr Bender whom I have heard discuss alcoholism has always used the so-called alcoholic wet brain the edema of the dura and pia arachnoid as the paradigm of what alcohol does to the rest of the human body If one assumes that in delirium tremens there is intracranial edema there is a ra tionale in attempting to reduce it by the use of a hypertonic solution You have also heard that Dr Wolff does not agree with that

Dr Wolff It does not matter whether I agree with it or not I

don't believe it has been demonstrated. I would also like to know whether there has been any evidence to the contrary.

Dr. Gold: How do we now stand with regard to the precipitation of delirium tremens by the withdrawal of alcohol?

Dr. Rennie: It is my impression that more patients with delirium tremens are precipitated into it by the abrupt cessation of taking alcohol than those who develop it during the course of the continuous use of alcohol. One sees it occasionally on a surgical service after a patient who has not been recognized as an alcoholic has had an operation. Following the operation, with abrupt withdrawal of alcohol, one may get a delirious patient.

Nevertheless, we withdraw alcohol abruptly. These are our reasons. If the patient already has delirium tremens, there is no problem of inducing delirium. If the patient is a chronic alcoholic, but has not developed delirium tremens, we take the chance that he can, with adequate medication, avoid delirium. As I remember, some ten years ago in a large series, *I think* at Bellevue, or perhaps at one of the state hospitals, in several thousand cases alcohol was abruptly withdrawn, and, in another large group, the patients were tapered off. There seemed to be no significant difference in the incidence of delirious reactions in the two groups.

Dr. Gold: Wortis wrote a paper a few years ago on his experiences at Bellevue in that connection. He said there was nothing to the idea of precipitating delirium tremens by the abrupt withdrawal of alcohol. He used as evidence the experience there, in which it was found that very few cases of delirium tremens developed on the wards when the withdrawal was abrupt.

Dr. Wolff: It is only fair to say that a certain number of people stop drinking as the first manifestation of their delirium tremens. This may prove misleading; some may interpret it as signifying that the cessation of alcohol intake causes the

symptoms of delirium that follow Would you care to comment on this point?

Dr Rennie I think that that is probably true

Dr Walter Modell Dr Rennie, you expressed a fear that in alcoholics there was a danger of dependence on sedatives, on the barbiturates and especially in the case of chloral hydrate

Dr Rennie I did not mean it was greater than in other addicts It is the tendency of alcoholics to lean on props

Visitor I would like to ask Dr. Rennie if he had any explanation of why the hallucinations of delirium tremens are so terrifying while hallucinations induced by other drugs may actually be amusing or pleasant

Dr Rennie They are not invariably terrifying in delirium tremens I have seen patients in delirium tremens who were vastly amused by the parade of bugs across the wall It need not be, although most commonly there is a fear reaction Why that is, I don't know Do you, Dr Wolff?

Dr Wolff I have examined 106 people with delirium from 27 different etiologic agents, and I could not see that the precipitating cause made much difference in the content of the delirium It happens that delirium is commonly induced by, or associated with, the use of alcohol (in 30 of the 106 patients I studied) It also happens that many people are frightened when things become unreal They get shaky when they have visual hallucinations But there are some who can look with detachment upon such things, just as they can look at other deviant circumstances in their lives I think that the reaction depends on the temperament and experience of the patient, and is a highly individualized matter

Dr Gold I wonder if Dr Rennie would say something about that strange mixture which is used to produce vomiting Why a mixture of pilocarpine and emetine? Why ephedrine should also be used I cannot understand It seems to me that there ought to be much simpler ways of producing sustained nausea A few teaspoonfuls of syrup of ipecac will make people

pital but on a farm where they worked all day, contributed to the life of the group, and where they had only fellow alcoholic patients as companions.

Obviously, the percentage of cures depends on a number of factors. What is the fundamental cause of the disorder? Is it a relatively reactive condition amenable to direct attack, or is it so deeply ingrained in the personality makeup of the individual that it requires a long, devious, intensive psychotherapeutic exploration? Does it occur as a symptom in a well integrated, well-organized, successful individual, with many assets to draw upon, or does it occur in a so-called psychopathic personality, unstable and undependable, and lacking in rational goals? Personality makeup makes a tremendous difference. The duration of disability makes a difference, as does the age of onset or age in which the condition reaches its peak. All of these factors may affect prognosis.

The skill, integrity, and sincerity of the therapist make a still greater difference in prognosis. The man who claimed the 85 per cent cures which I just mentioned is one who very early in his career of treating of alcoholics felt that he had to give up drinking himself, that he could not hope to be sincere and to sell a patient the idea that a nondrinking life could be useful and constructive if he were having cocktails at dinner. He is now convinced that unless one is a nondrinker one cannot be a good therapist of the alcoholic.

The Alcoholics Anonymous group rely very heavily upon an inspirational quality of therapy which is woven into a religious consideration of the power of God in giving strength to these people. Something of the same kind of fervor marks the personality of a good therapist of an alcoholic.

Dr. Wolff: The hour is up and we shall have to end our discussion.

SUMMARY

Dr Gold The conference this afternoon dealt with one of the major causes of ill health Addiction to alcohol is estimated to interfere with normal behavior and performance in about 2,500 000 people in the United States The disability is of varying degrees and in about 200 000 it presents a serious and incapacitating disorder Alcoholism is a chronic disease which runs a variety of courses and shows a marked tendency to recurrence

Broadly speaking, the cure of alcoholism involves two problems one, the correction of a personality defect which leads to the chronic abuse of alcohol, and two, the management of disturbances which result directly or indirectly from the alcohol itself

Strong emphasis was placed on the current viewpoint that individuals who take to the chronic use of alcohol are psychologically ill, unable to function harmoniously without it. They fall into various groups as represented by the spree drinkers," and varieties of steady drinkers' in whom the use of alcohol may be a symptom of an underlying psychiatric disorder such as a depression, or who take to alcohol for relief from emotional conflicts or intolerable stresses

It has become clearly manifest that the common devices employed by general practitioners in the care of these cases as ambulant patients living under their customary conditions are by themselves not sufficiently effective to deserve serious consideration A wide variety of systems for management have been employed with varying degrees of success all laying major stress on the problem of psychologic readjustment of the victim of this disease

Mention was made of the appropriate use of expert psychotherapy, the rôle of hospitalization group psychotherapy, electric shock therapy, conditioned reflex therapy, intervention of social agencies Alcoholics Anonymous, the Yale Clinic Plan,

interesting view that an inspirational quality prevails in the most successful management of the alcoholic, and that such fervor may be wanting in the case of the therapist who habitually takes cocktails at dinner.

The Rational Use of Cathartic Agents, Part I

Dr David P Barr Today we shall discuss the use of cathartics from the point of view of rational therapeutics

When I started work in medicine we used cathartics liberally, and it was the custom in Bellevue Hospital, when I first entered it, to give to every new patient who was not moribund a "three-by ten," or 3 grains of calomel and 10 grains of sodium bicarbonate To the alcoholics we gave a "five by fifteen," which was 5 grains of calomel and 15 grains of sodium bicarbonate The entire range of cathartics was at our disposal, from the mild glycyrrhiza to the powerful oleum tiglii The first gross error which I made in the use of these drugs was confusing the doses of glycyrrhiza and jalap The difference in dose was only eight fold but the difference in effect was extraordinary We learned at that time that there was such a thing as the abuse of cathartics and this thought has so thoroughly infiltrated the minds of physicians that some have almost forgotten that there is a use for these agents

Dr Travell will open the discussion today

Dr Janet Travell I think that the medical profession may appreciate the abuses of cathartics more than the public does If one judges from the advertisements, these compounds are more widely used than any other class of pharmacologic agents In spite of this the answers are lacking to a great many questions of therapeutic importance, questions relating to potency and dosage, and to the matter of tolerance For example, we do

movement of material from the colon into the rectum. It has been demonstrated in animals that liquid petrolatum is absorbed from the gastrointestinal tract and is deposited in the liver.

Phenolphthalein has been reported to cause a variety of toxic effects including skin eruptions and renal irritation. Dr. Loewe has had special experience in the use of phenolphthalein and I should like to leave this topic for him to discuss. However, I should like to point out that hypersensitivity to the cathartic action of this drug may be encountered, causing excessive purgation after an ordinary therapeutic dose, with sequelae amounting almost to collapse. Even in the average person, the ordinary dose of phenolphthalein often has prolonged effects which extend over 2 or 3 days.

The magnesium salts undergo considerable absorption and may cause a rise in the blood level of magnesium, especially if the excretion of this ion is restricted owing to renal damage. If given in hypertonic solution, they may cause vomiting. The saline laxatives should therefore be given in isotonic solution. In the case of the U.S.P. salt of magnesium sulfate, a 4 per cent solution is approximately isotonic. In considering the salines, perhaps it should be mentioned that the tartrates have been shown to exert a nephrotoxic action in animals.

Griping, or cramps, may present a problem in the use of cathartics. This disagreeable side-action is supposed to be counteracted in the case of aloe by the other ingredients of the familiar A.B. and S. pill; aloe is given to stimulate intestinal motility, belladonna is given as an antispasmodic, and strychnine is included for its "tonic" effects on the gut. Pharmacologically such preparations are ridiculous. The anthracene compounds are excreted in the milk and may cause diarrhea in the nursing infant. Calomel may give rise to mercury poisoning. The strongly irritant cathartic drugs may cause violent irritation of the bowel and abortion.

If one takes into consideration all of these dangers and difficulties what does one do if one must give a cathartic to relieve constipation? In *acute* constipation, the cathartic of choice is the suitable dose of any one which will produce a prompt and complete evacuation without excessive purgation A watery stool is usually desirable under these conditions Magnesium sulfate or magnesium hydroxide (milk of magnesia) are usually preferred At times, the use of an enema is often more rational than a cathartic, if the trouble lies in the lower end of the intestinal tract In *chronic* constipation, the choice is again the appropriate dose of any one which will regularly produce a soft, formed stool rather than a watery evacuation The gums seem to be the most satisfactory agents for this purpose Cascara senna, sodium phosphate (the disodium salt), and milk of magnesia are also frequently used over long periods of time Owing to the ready adaptation of the bowel to new stimuli it is often necessary to alternate one cathartic with another, and, therefore, several cathartics should be included in your therapeutic armamentarium

Dr Barr Dr Heffner will continue the discussion

Dr Reid R Heffner At the previous conference we discussed the indications for and the actions of a number of the well known cathartics, but our remarks about the so-called bulk producers were confined largely to agar Since these bulk producers or colloid laxatives, occupy an important place in the treatment of constipation, we shall discuss their action in some detail Fortunately during the past few years several studies have been carried out in animals and in humans which shed light on the choice of a bulk producer

In this hospital we used to prescribe agar frequently in the treatment of chronic constipation without much thought about its merits as compared with some of the other colloids Now, with changed world conditions making agar difficult to obtain, we have been forced to prescribe some of the other

members of this group In our experience most of them are superior to agar, and that opinion is in line with the experimental evidence

A number of colloid laxatives, or gums, are available for clinical use under a variety of trade names Gray and Tainter in 1941 made a useful classification of these substances In one group is colloidal clay, from which a commercial product Elkonite, is obtained I believe that this is not available for clinical use In the next group is agar As you know, agar is a mucilaginous substance which comes from sea algae which are found along the eastern coast of Asia It was introduced by Schmidt as a laxative in 1905 Its action is not essentially different from that of other gums. Next are the mucilages derived from kelp, which exert the same type of action as agar and which are typified by the commercial product Kelgin Acacia acts likewise, but is not used much for its laxative effect. The members of the tragacanth group are closely related to gum acacia However, the powdered form differs from acacia in that it swells readily in cold water Tragacanth contains about 10 per cent of gum arabin or tragacanthin, together with about 60 per cent of the insoluble gum, bassorin Bassorin swells to a large bulk in water In the same group are the karaya and bassora gums, which consist mainly of bassorin These gums differ from the true mucilages in that they swell up as large granules rather than as a soft mucilaginous mass These tragacanth granules do not tend to stick in the teeth and can be easily swallowed if washed down with water The plantago gums or psyllium seed preparations have been used as laxatives in the Orient for over a thousand years This group is said to supply roughage and promote peristalsis through mechanical irritation Several proprietary preparations are available for clinical use, among which are Mucilose, Metamucil Serutan and Siblin

Bastedo summarizes the experiments on the relative hydrophilic potency of the gums as follows When the degree of

swelling of flaked agar in water was taken as 1, granulated agar was 3, powdered agar 5½, whole psyllium seeds 10, hulled psyllium seeds 14, and bassorin 29

From the experiments in animals and in humans, as carried out by Parsons, Ivy, and Isaacs, and Gray and Tainter, it seems that the tragacanth group of colloids passes through the intestine unchanged and owes its laxative properties to its marked ability to imbibe water Although processed psyllium products possess this colloidal power to a lesser degree, they are, in addition, partially broken down to irritating end products, which are incompletely absorbed and do not increase significantly the dry weight of the stools These irritant substances, however, do increase the water content of the stool as a result of the more rapid passage of material through the intestinal tract.

When a colloid laxative is prescribed, large quantities of water should be taken in order to prevent impaction These agents should be used with caution in the aged and in debilitated patients There are a number of reports of impaction at various sites, ranging from the esophagus down to the rectum, after administration of psyllium seeds and other gums

Sensitivity to karaya gum has been reported The manifestations may be hay fever, asthma dermatitis, or gastrointestinal distress

In stubborn cases of constipation, the addition to the gum of small amounts of other laxatives, such as cascara is frequently prescribed for a short time Several of the commercial tragacanth granule preparations such as Karajel and Mucara, are reinforced with cascara A bedtime dose of the emulsion of liquid petrolatum may enhance the action of the gum Liquid petrolatum (60 to 90 cc) as a retention enema at night is often used for short periods in obstinate cases

We all know that dried and fresh fruits as well as cooked fruits are helpful not only in mild cases but as an adjuvant in stubborn cases of constipation Their action depends upon

two principles. The first is that the unabsorbable carbohydrate exerts a certain amount of osmotic pressure and thus increases bulk by retaining water. The second is that the indigestible residue, or roughage if you like, produces mechanical irritation of the intestine and thus stimulates motility directly.

There is no good experimental evidence to warrant the routine addition of vitamin B_1 to any laxative preparation. It is true that the intestine is supposed to be atonic in thiamine deficiency, but in the ordinary case of constipation without avitaminosis, thiamine is not helpful. Dr. Loewe has been interested in the effect of this vitamin on intestinal motility and can give us firsthand information about his experiments.

Dr. Barr: Dr. Loewe, you have been quoted this afternoon, and we should like to hear from you.

Dr. W. S. Loewe: In our experiments in the monkey, vitamin B_1 showed no capacity for increasing the laxative effect of phenolphthalein, and such drug combination accordingly shows no promise for the treatment of constipation.

I would like to discuss the problem of constipation as illustrated by other observations in monkeys. The first point is that the administration of a laxative may result in constipation. With the aid of continuous daily stool records, I studied the incidence of stool-free days in more than 300 monkeys during a period representing 118 years of monkey life. Originally this study was undertaken in the search for constipated monkeys to serve as test objects for assaying the potency of laxatives. It was found that spontaneous constipation is extremely rare in monkeys, and that such attacks of constipation as do occur almost never last longer than one day. In these 118 years of monkey life, only 2 per cent of the days showed an absence of stool, and it is interesting that 86 per cent of these constipation-days occurred after the administration of a laxative, that is, as the aftermath of the laxative effect. This phenomenon was discussed in one of these conferences a few years ago, when Dr. Martin showed by X-rays in patients that after vigorous ca-

tharsis the lower intestine is empty These observations both in the monkey and in man may be explained as a consequence of emptying the bowel of fecal material

Only the Rhesus monkey gives a response to laxatives which is qualitatively and quantitatively comparable to the effect of these agents in man When the purgative potencies of a series of drugs in the monkey were compared with the anticonstipating potencies of these same drugs in patients the sequence of potencies was the same in the monkey and in man To determine such a parallelism is an essential requirement for a bio-assay method although it is often neglected

Many attempts have been made to test laxatives in species other than the monkey For instance some investigators observed that in a transparent water flea the entire intestinal tract and its motility are visible and hence concluded that this must be an excellent test object for laxatives They did not take into account the enormous species differences in the physiology and pharmacology of the intestinal tract which distinguish all species of animals cats and dogs as well as water fleas from man The Rhesus monkey seems so far to be the only exception to this rule Another example of inadequate bio assay is the recent use of guinea pigs for testing anthraquinones which were formerly tested in cats In both instances the results were unhesitatingly considered to apply to the therapeutic action of these drugs in man When we compared these results with those obtained in the monkey we found that some of the anthraquinones which were strongly active in guinea pigs or in cats were ineffective or poorly effective in our experiments in monkeys and vice versa Those which I found effective in the monkey are those which are for the most part used in human therapy

Our experience was similar when we tried to reproduce in the monkey the classic work which Abel and Rowntree did on phthaleins in dogs They found for instance that phenoltetrachlorphthalein was about as potent as phenolphthalein in

the dog, whereas I found it without any laxative effect in the monkey, it has since also been shown to be ineffective in man Also, thymolphthalein and isophenolphthalein, which were suggested as laxatives on the basis of tests in other species of animals, in our monkey experiments were disclosed to be virtually ineffective

As for the mechanism of laxative action one can only speak of makeshift explanations at the present time One of these makeshifts is to consider such phenol derivatives as anthraquinone and phenolphthalein as phenols, and to attribute to them the local irritant properties of phenol itself In fact none of the laxative phthaleins, which I know, has any demonstrable local irritant action Even undiluted phenolphthalein when powdered into the eye does not cause local irritation When injected subcutaneously in gram doses in a rabbit, it causes no local reaction, it behaves like an entirely inert deposit of foreign material The reason for this makeshift theory of purgation by local irritation is, of course, that there is no other obvious explanation Certainly, the mechanism of the laxative action of the phthaleins is not a simple one that can be explained by a motor response of a surviving intestinal strip to added phenolphthalein

From an entirely different approach I recently studied the one chemical reaction which is characteristic of both the anthraquinones and the phenolphthaleins Both have an oxygen group, ketonic or lactonic, which can be replaced by the nitrogen of ammonia or of primary amines resulting in the formation of imido derivatives This tendency of the various phthaleins to form imido derivatives interested me as a possible basis of detoxification of phthaleins in the body since there are so many amino groups available in every biologic substratum The results of measurements of the 'imido affinity of a series of hydroxy diphenylphthalides performed with Hubacher, Doernberg and Horner were entirely unexpected Phthalein number 1, for instance, in arbitrary but comparable figures

had a laxative potency of 0 3 and an imide affinity of about 4, number 2 had a potency of 0 68 and an affinity of 21 number 3 had a potency of 1 and an affinity of 34 and number 4 had a potency of 1 63 and an affinity of 52

If a chemical reaction of this kind plays a rôle in detoxifying phthaleins in the body the affinities should be reciprocal to the potencies Instead there is a clear cut parallelism between laxative potency and imide affinity This suggests that imide formation by reaction with some primary amine of the tissues may represent an important link in the mechanism of laxative action of these drugs This concept is far from being proved conclusively But I believe that it is a stimulating hypothesis because it brings the trend of ideas away from existing make shift concepts and draws attention to the possibility that a specific reaction between the drug and some body component may be the basis of the mechanism of action It would explain the enormous species differences in sensitivity and it would relate the action of two groups of phenol laxatives phthaleins and anthraquinones to one and the same mechanism

Such an hypothesis would also do away with the particularly vague idea that being irritant phenols the phthaleins should be considered toxic whereas in reality they appear to be quite harmless This latter fact may be stressed because the assumption has been aired repeatedly that phenolphthalein is toxic to the kidney I believe this is based on the assumption of local irritant properties If phenolphthalein were a local irritant then it might indeed irritate the kidney if it were to appear unchanged at this site of excretion Therefore whenever kidney damage coincides with the use of phenolphthalein there is a great tendency to assume a causal relationship I have been eager to see somebody take the bull by the horns and try phenolphthalein in individuals with kidney injury Of course a deliberate experiment of this kind is not possible But when kidney function was studied after a thousand doses of phenolphthalein given to patients as well as to healthy individuals

there was no indication of kidney injury by phenolphthalein. On the contrary, in a number of individuals in the group who had a disturbance of kidney function prior to the dose, the existing albuminuria was found to be less after phenolphthalein than before.

Dr. Barr: The meeting is now open for comments and questions.

Dr. Charles H. Wheeler: I would like to ask Dr. Heffner how one decides between a laxative like cascara and one of the bulk-forming gums in the treatment of a particular patient.

Dr. Heffner: I cannot answer that specifically. One has to use the trial and error method. If possible, we like to get away from the so-called habit-forming laxatives, if there are such things.

Dr. Barr: Are there not?

Dr. Heffner: Perhaps, in some cases, but there is debate whether a tolerance to cascara can be built up or not.

Our procedure is usually to try first one of the bulk producers, adding large quantities of fluid plus other details of the general management. Then, if necessary, we give one of the stronger cathartics, such as cascara, milk of magnesia, or one of the phosphates. Not that it does any harm to the bowel to use the stronger laxatives, but the patient usually objects more to taking one of those laxatives than he does to taking a bulk producer. Also, we must be guided in our choice of a laxative by the way the individual tolerates the preparation.

Dr. Barr: I should like to ask a very practical question. On the cathartic rounds of my intern days, I had approximately 30 different products and preparations from which to choose. This was very confusing, because it seemed that it might take a lifetime to master the knowledge of the cathartics available. I am wondering, Dr. Travell, if you could give us any idea of how many of these preparations you feel are at all necessary in the practice of medicine today.

Dr. Travell: I think that there are relatively few. You might

include in your inventory one or two of the gums with which you are familiar, magnesium sulfate, milk of magnesia, and disodium phosphate as representatives of the saline cathartics, cascara in the form of tablets and fluid extract, compound powder of senna for those who prefer it to cascara, and, possibly, castor oil in selected cases. That is probably all that you really need. You might add phenolphthalein if you like, but I do not prescribe it.

Dr. Wheeler: No mineral oil?

Dr. Travell: I think mineral oil is not essential. The present trend is to do without mineral oil for many reasons. But if you must use it, you will probably obtain a better laxative effect by using an emulsion of liquid petrolatum rather than plain liquid petrolatum. It has been shown that the emulsion is more miscible with the organic matter in the stool. The *United States Pharmacopœia* emulsion of liquid petrolatum is an extremely palatable preparation which is not reinforced with one of the irritant cathartics.

Dr. McKeen Cattell: Why did you name more than one saline cathartic?

Dr. Travell: Largely because of the matter of preference by the patient. One patient may object to the taste of Epsom salts and another to the taste of milk of magnesia. Disodium phosphate in average doses is not as vigorous a cathartic as the magnesium salts I mentioned. It produces a soft and formed, rather than a watery, evacuation, and probably has a certain place in the treatment of chronic intestinal stasis.

Dr. Cattell: Is that difference in effect not a matter of dosage?

Dr. Travell: Yes, probably it is a matter of dosage, but it is so fixed by tradition that it seems to be easier to vary the drug than the dose. Then, too, there still remains the problem of palatability.

Dr. Harry Gold: At this point, I should like to say a few words about the choice of cathartic agents, and the reason for their choice. Generally speaking, I believe that the patient

who is in need of a frequent or even daily cathartic because of chronic constipation will do best to take one of the emodin agents, namely, cascara, senna, rhubarb, or aloe. He takes the dose at night and he is likely to have a bowel movement in the morning. The reason for using it this way is that it takes 6 or more hours for the material to reach its site of action and for the elaboration of the active principle, and if he has taken it during the day, it is possible that its effect might awaken him at night. I do not believe there are any persons whose bowels cannot be made to move by this group of agents provided the dose is large enough. Therefore, if one starts with any one of them, it would be unwise to abandon it for lack of action until one has explored a reasonable range of dosage. The reason for having more than one of these emodin cathartics at one's disposal is that these resins are mixtures of varying composition, some containing more tannin and other principles, which contribute to a favorable or unfavorable result in some patients. There are some patients in whom one of these drugs either produces no effect or, when the dose is increased sufficiently to produce an evacuation, gives rise to abdominal cramps. With another member of the group, it is often possible to widen the margin between the laxative action and the griping action, so that when this unfavorable situation is encountered with, let us say, cascara, one might explore the possibilities of using aloe. I think we should never forget that all laxative agents may produce griping if the doses are too large, and that the first step in the escape from griping is not to shift to another preparation, but to attempt to adjust the dosage of the preparation which is being used.

In regard to the saline cathartics, while they can be used for the same type of condition as the emodin cathartics, they are particularly applicable to a special type of constipation problem. They are especially useful for the patient whose bowel movements seem to follow the law of diminishing returns, who finds himself at the end of a week with inadequate evacuation

and a sense of general discomfort which, in his experience, is relieved by a satisfactory ' cleaning out " He discovers this discomfort when he arises in the morning The emodin cathartic is not suitable for this problem because it takes too long to act. Such a patient does better by taking a saline cathartic which produces a response very quickly, much like the response to an enema in somewhere between ½ to 2 hours, if an adequate dose has been taken and with sufficient water to make an isotonic solution I do not know why we continue to use Epsom salts or Glauber salts, which have a perfectly awful taste, when disodium phosphate is very pleasant to take, and if the dose is large enough, produces an equally satisfactory response I would recommend the most palatable preparation of this salt containing also some tartrate and citrate, namely, the effervescent sodium phosphate U S P A dose of 15 Gm or 6 teaspoonfuls of the granules dissolved in a glass of water, followed by another glass of water is extremely effective The patient should learn how much he needs by reducing or increasing that dose I doubt very much that there is need for any more than this one saline cathartic What we do need is greater attention to the adjustment of the dose to the need of the individual case The problem here is the same as that for so many other drugs we spend more time shifting from one preparation to another than we do solving a more basic problem, determining the needs for the individual case

There is one point about mineral oil which has not been mentioned, namely, the problem of the individual with a mild form of constipation in whom the chief problem is spasm of the rectal sphincter with or without sore hemorrhoids or fissure There is no cathartic agent which quite fills the needs in such a case so well as appropriate doses of mineral oil

A word about magnesium sulfate I do not believe it is generally realized that as much as about 40 per cent of a dose of magnesium sulfate used as a purgative is absorbed This produces a negligible rise in the blood magnesium in normal per-

sons because it is so rapidly excreted. Dr. Hirschfelder published a study in 1934 in which he showed that in patients with nephritis, the magnesium level of the blood plasma may rise from the normal of about 2 mg. to 11 mg. per 100 cc. of plasma after 20 to 30 Gm. of Epsom salts, and that such doses may produce drowsiness verging on coma. He further pointed out that blood levels of 5 mg. of magnesium in animals render them extremely sensitive to ordinary doses of morphine. I recall Dr. Barr referring to the danger of morphine in the uremic patient at one of our previous conferences. Dr. Hirschfelder's paper refers to what may be the origin of that observation, namely, Osler's statement that patients with nephritis and very old persons should receive morphine with caution; the favorite saline purgative on his wards at Johns Hopkins was Epsom salts.

Dr. Barr: There are several matters concerning the use of cathartic agents which should be considered, but our time is now up. Perhaps we might continue this discussion at the conference next week.

The Rational Use of Cathartic Agents, Part II

Dr Harry Gold: The conference last week dealt with the subject of the rational use of cathartic agents Consideration was given to the choice of cathartic agents for particular problems, the methods of bio assay of these agents, the rôle of cathartics in the cause as well as in the relief of constipation, the actions of the gum laxatives, the irritant laxatives and the salines, their mechanisms of action, the problem of griping after cathartics, and some of the toxic effects which are not commonly considered in the routine use of Epsom salts There seemed to be several points of interest in need of further discussion, but the time was too short to take them up We hope to be able to explore these matters in the conference today.

Dr Kirby A Martin In relation to Dr Heffner's discussion, I wish to point out that one should differentiate between bulk and roughage The literature is confusing on this point, since some authors use the terms interchangeably A stool may be large or small in volume depending upon the amount of cellulose in the food It may be smooth or rough depending upon the kind of cellulose consumed

A few years ago Olmsted classified the cellulose content of a few of the common vegetables into cellulose, hemicellulose, and lignin For example the pulp from sugar beets carrots, and cabbage is composed of hemicellulose This substance is hydrophilic, and in the intestinal tract it supplies an increased bulk to the stool that is smooth and resembles the effect of

eating. Separation from food is, of course, important in order to minimize the loss of the fat-soluble vitamins which Dr. Travell has mentioned. Some patients get along well on the use of a simple tap-water enema, taken every 3 days if necessary.

It is the general opinion at present that, in the majority of patients with spastic constipation, the primary exciting cause of disturbed bowel function is nervous tension, and the first consideration is to remove the cause of the nervous tension with psychotherapeutic devices, which might be termed "emotional catharsis." To reduce the irritability of the bowel directly, first, provision should be made for a low-residue diet to reduce the bulk of the fecal mass, and second, unnecessary irritation of the colon from spices, pepper, and sauces, and especially from laxatives, and irritant enemas should be avoided. Jacobson has shown that the tone of smooth muscle is in some way related to the tone of skeletal muscle, and he has had some success in alleviating states of hyperirritability of smooth muscle, such as an irritable colon, by routines which establish skeletal-muscle relaxation. This can be accomplished by physical therapy of the type available in the hospital, and also by homemade physical therapy in the form of tepid tubs and unskilled massage. Relaxation may be further augmented by mild regular exercise. Finally, the use of antispasmodics, such as belladonna and syntropan, or the use of mild sedation with phenobarbital, has, in the belief of many physicians, been attended by additional improvement in spastic constipation.

I know that many experienced doctors use agar, psyllium seed, and other such substances in spastic constipation, in order to provide smooth bulk. I have never tried this myself because I could not see the physiologic basis for it, since we are actually trying to diminish the stimulus to reflex hypermotility.

Dr. Janet Travell: There are two kinds of intestinal motility, first, the propulsive type, and second, the segmental or

tonic contraction and it is quite possible that an increase in bulk may increase peristalsis without increasing spasm The stimulus which normally initiates the propulsive wave is probably stretching of the muscle fibers of the gut

Dr Gold Let us see if we have that straight Dr Almy would not use bulk in so-called spastic constipation because that tends to increase the stimulus to the gut which is something he tries to avoid Dr Travell s point is that if the stimulus is a propulsive one bulk might not be contraindicated in this type of constipation

Dr Sydney Weintraub Are we not confusing bulk and roughage? I think that in the spastic colon it is not a question of how much bulk there is but a question of how coarse the residue is Don t you agree with that?

Dr Travell That is exactly my point Increased bulk if it is smooth may stimulate peristalsis whereas if it is rough it may act as an irritant and set up spasm

Dr Weintraub And we usually give agar and similar materials to increase the bulk because it produces not roughage but smoothage as Dr Martin calls it

Dr Almy I would say that roughage is obviously contraindicated but one may also see reactive spasm in the constipated bowel after two very bland agents which cause distention one is barium and the other is air introduced through the proctoscope

The simple blowing of air into the rectum of the patient with spastic constipation will often result in so much spasm that one cannot get past the rectosigmoid junction I wonder therefore if the distinction which you have drawn between the effect of smooth bulk and rough bulk is valid?

Dr Travell Sudden distention of the gut by blowing it up with air might produce an entirely different effect from the gradual distention which follows the introduction of material by mouth

Student Dr Almy spoke of the use of antispasmodics in

definitions that I found, and I won't waste your time in doing so.

I would prefer to answer this question another way. It is helpful to regard constipation as a change in the bowel rhythm. A disturbance in function may manifest itself in three ways: first, as a change in the rate of flow, that is, either diarrhea or constipation; second, as a change in the character of the contents, that is, an increase or decrease in fluid; or third, by the presence of blood, mucus, or pus. It should be noted that the spastic colon may result in either diarrhea or constipation.

Dr. Lawrence W. Hanlon: Hurst says that the patient usually regards himself as constipated because he takes physics, and is really suffering from "a self-induced diarrhea." He describes the sufferers as hypochondriacs who have their own idea of ideal stool size, and must learn there is no standard size, shape, color, or consistency. He says that they "should learn to follow the example of the dog instead of the cat, and never look behind them."

Student: How long may a patient go without a bowel movement and still be considered normal?

Dr. Martin: We had a 17-year-old boy who had normally a rhythm of one bowel movement every 14 days, who was brought to the clinic by his mother. A gastrointestinal X-ray series was reported as normal after castor oil preparation. Motor meal studies after 1, 3, 5 and 6 hours, as well as a barium enema, showed nothing abnormal. We were unable to get further studies. This patient was entirely satisfied with the situation and had no symptoms.

Dr. Almy: I think cases are recorded in the literature in which patients have gone 6 months without a bowel movement and did not come to any violent end.

Dr. Travell: Reports on survivors on life rafts in the Pacific contain accounts of many weeks without a bowel movement.

Dr. Gold: It would almost seem as if having a bowel movement is not essential.

Dr Martin Dr Hauser made a report on the people on life rafts and many of them had a normal movement every day, even though there was no food That is easy to understand if you appreciate what the bulk of the stool is made up of one third bacteria, one third secretion, and probably one third food residue If you cut out one third by the absence of food, the remainder may still be enough for a sizable stool

Dr Weintraub Actually, constipation of itself does not hurt most of these patients, but it is their reaction toward constipation, induced by what they read about it on the subway cards and what they hear over the radio as to the terrible things that happen to people when they are constipated that is harmful They are told that they are full of poison, and they begin to believe it and worry about it That is the point that Dr Almy tried to bring out about why these people come to the doctor and to the clinic seeking relief It is because of their fear Constipation has been regarded as a colonic manifestation of a psychoneurosis, and I think that just about defines it.

Dr Gold I should like to ask Dr Almy again what he does specifically to relieve the constipation in a patient in whom, for one reason or another, dietary regimen exercise, and psychologic measures have not solved the problem

Dr Almy In the hospital we do leave a standing order for milk of magnesia and mineral oil if necessary If that is ineffective, we use an enema

Dr Gold What does one do in the out patient department, or in the cases of ambulant patients one sees in the office?

Dr Almy The enema is still the best answer

Dr Gold The patient might have to take one 3 times a week Is that all right?

Dr Almy Yes

Dr Martin Dr Bastedo, in reviewing the subject a few years ago said, Why upset thirty five feet of intestine when the trouble is within eight inches of the rectum? As Dr Almy has

pointed out, the use of an enema is often more rational than a cathartic

Dr Cattell Does not constipation usually take care of itself?

Dr Almy It depends upon how willing patients are to follow advice Many patients are incapable of accepting the idea that they may go more than one day without a bowel movement Sometimes they will never restore the normal pattern of their bowel function because they are afraid

Dr Gold What proportion of patients who complain of constipation end up, after you have prescribed dietary regulation extra fluid, bulk factors, and psychotherapy, *still having constipation*, and need a laxative for relief?

Dr Weintraub I would say very roughly, based on experience in private practice, at least 25 per cent, or maybe more These patients may follow a particular regimen without a cathartic *for a while and it may work But then they* seem to let down, they stop taking the agar and stop exercising One day, they decide they need a good cathartic and take one and then the whole cycle is started all over again There is no bowel movement for 2 or 3 days after the cathartic so they take another dose and finally return with the story, ' I am back to my old bad habits ' Then I have to start explaining things and putting them on the regimen all over again

Dr Gold I should like to ask the question *in another form* In what proportion of the chronic constipators that come to your office do you prescribe a laxative?

Dr Weintraub As a rule only to elderly people, who have taken cathartic pills all their lives and who have found that if they take 10 or 15 grains of cascara or some other favorite pill they get along all right

I have learned from experience that it is usually hopeless to try to put these people on a non cathartic *regimen* so we allow them to take their pills

In the younger people and intelligent people however, one can correct constipation by physiologic measures

Dr. Gold: When you say you allow them to take their pills, you mean you don't change the preparation?

Dr. Weintraub: I don't change it.

Dr. Gold: There is no basis for choice among the pills for chronic constipation except the patient's own experience and preference?

Dr. Weintraub: That is right.

Dr. Martin: Dr. Almy expressed a preference for milk of magnesia. We have found that milk of magnesia produces cramps in many instances, and that cascara is better tolerated by the spastic colon.

Dr. Almy: Why is cascara preferable to milk of magnesia?

Dr. Martin: Because in average doses it does not ordinarily produce cramps.

Dr. Gold: There is the point that cascara exerts its effect by virtue of local irritation in the large bowel, while milk of magnesia, like salines, acts through osmotic retention of water, and the effect is that of bulk. I am certain that cramps may be caused by all of them if the doses are large enough. Is drinking water of any value in constipation?

Dr. Martin: I have never observed that, within normal limits, the amount of water a patient takes has any effect on constipation.

SUMMARY

Dr. Travell: The discussion this afternoon and in our conference last week dealt with one of the common problems of everyday practice, namely, the use of cathartics. Among the various topics were these questions: When is a patient constipated? Is constipation a matter of frequency of stool, quantity of stool, or consistency of stool? How much validity has the classification of spastic and atonic constipation? Should constipation be allowed to right itself or should patients be encouraged to do something about it? When should one resort to laxa-

tive agents? What is the basis for a choice among laxative agents?

These and related questions were explored in the endeavor to crystallize a more rational system for the management of constipation problems than seems to be the general practice

A satisfactory definition of constipation appears to be difficult to obtain Perhaps the one which defines it in terms of a deviation from the individual's own bowel rhythm comes nearest to the true description of the constipated state The view was expressed that the vast majority of cases of constipation are spastic and that so called atonic constipation is only rarely encountered, and then, usually, in relation to organic disease

That constipation is in large measure a state of the mind is widely accepted Patients have come to regard a deviation from their usual bowel rhythm with apprehension, and the harm which results from constipation seems to be largely a fear of harm and an anxiety concerning it, rather than actual damage to health Emphasis was placed on the need of educating the patient who complains of constipation with respect to the hygienic measures likely to lead to more regular bowel action, namely, systematic habits, diet, physical exercise, and psychic reactions

The numerous types of laxative agents were considered, namely, the irritant cathartics like cascara senna, or phenolphthalein, the salines, the bulk producing gums and mineral oil While there is need for several cathartic agents the vast numbers of such agents and mixtures represent needless duplication and are a source of confusion

The few special indications for one or another of these agents were discussed but, for the most part, little is known concerning the mode of action, and the selection of a cathartic agent for any particular individual appears to be a matter of trial and error The patient s own preference is often allowed to play an important part in the choice of a cathartic agent Attention was directed to the view that, in most instances, the

dose is a more decisive factor in obtaining satisfactory results than the type of cathartic, for most of them appear to be capable of producing pain and griping in excessive dosage. It was urged that more effort be made to establish the proper dose of any one agent than to shift from one to another as a means of securing the best results. Habituation to cathartic agents occurs, and the use of cathartics may itself promote constipation.

There is great need for scientific comparisons of the potency of cathartic agents. Most animals are unsuited for such comparisons. The Rhesus monkey appears to respond in a manner similar to the human. The constipated human subject should be put to use more systematically than has been the case in the bio-assay of cathartic agents.

Treatment of Infections of the Genitourinary Tract

Dr. Charles H. Wheeler: The subject today is the treatment of urinary tract infections. As you know, the treatment of such infections as urethritis, prostatitis, cystitis, pyelitis of pregnancy, and pyelonephritis was unsatisfactory for a long time. Many substances and procedures which we used, namely, methenamine or urotropin, ketogenic diet, acidification, alkalinization, and mandelic acid did not work as well or as frequently as we would have liked. Today the outlook is better, and we shall see how matters stand.

Dr. Modell will open the conference with a discussion of some of the pharmacologic aspects of this field of therapy.

Dr. Walter Modell: The pharmacology of urinary antiseptics used to be an elegant subject for discussion because there were so many drugs to talk about. One could keep going for a long time discussing them and condemning them. But in recent years the subject has become much simpler and shorter, and from the patient's point of view, far more satisfactory. This is so because several very effective new agents have become available for the treatment of infections of the urinary tract, mandelic acid and its derivatives, the sulfonamides, penicillin, and streptomycin. The sulfonamides are the most important, but the others have their special uses, and there still may be occasional use for a much older agent, methenamine. While therapy has become so much more satisfactory, the problem of an early and exact diagnosis is still of paramount impor-

nce and must not be neglected because effective chemothera utic agents are avulable

Drug manufacturers are reluctant to bury their dead Some the ghosts which still haunt the advertising pages of our edical journals stem from the abandoned field of chromo-erapy There was a time when a common form of treatment urinary infections was essentially a matter of coloring the ine One could color it blue, green orange, or yellow, de nding largely on one s taste and, in some cases, on the kind professional samples which were lying around the office his was practiced rather widely until it became apparent to me more astute observers that the bacteria showed less inter-t in the color of the urine than did the patient Nevertheless, e dyes are still being used, although I believe that they are n their way out

One of the drugs, which has stood the test of time and which ould not be entirely forgotten in spite of the more effective wcomers is methenamine Helmholtz has shown that strains Escherichia coli which are resistant to the sulfonamides and andelic acid can be treated effectively by methenamine This ug therefore, still has a place although it is now a minor ne It is well to remember that methenamine is effective only n acid media in which it is broken down to liberate an effec-ve component. Concentrations of about 200 mg per 100 cc the urine are considered necessary the pH must be 6 or less r therapeutic effectiveness Concentrations of methenamine eater than 200 mg per 100 cc are irritating to the bladder, e therapeutic range, therefore is rather narrow

Mandelic acid was very unfortunate because although its iscovery constituted an important advance it occurred just efore that of the sulfonamides the powers of mandelic acid, ierefore never really had a chance to achieve wide recogni-on The discovery of this drug followed logically from the use f the ketogenic diet in the treatment of urinary infections nd was the result of a search for an effective hydroxy acid

which would not be metabolized by the normal body. Mandelic acid is effective in infections by Streptococcus faecalis, in which condition none of the sulfonamides is said to be useful. Mandelic acid must be present in the urine in concentrations of 0.5 per cent or over, and the urine must be decidedly acid, with a pH of 5.5 or less for this drug to be effective. The chief disadvantages of mandelic acid are its taste, which is exceedingly difficult to disguise, and the fact that it must be taken with a strong acidifying agent. In connection with the use of mandelic acid, it is well to modify the diet so as to insure an acid ash. There are still instances in which the sulfonamides are not effective or may not be used; in such cases, the use of mandelic acid or its derivatives may be considered.

The sulfonamides have, of course, completely overshadowed the field of the therapy of urinary infections. Today, I think we can consider only two members of this group as being of prime importance: sulfadiazine and sulfathiazole. Sulfanilamide and sulfapyridine have been shown to be less effective than these. Another member, sulfacetamide, was said to be of particular value in urinary infections. However, in an article from the Mayo Clinic entitled *The Bacteriostatic Action of Sulfadiazine, Sulfathiazole, Sulfacetamide, and Sulfapyridine in Bacteria Isolated from Urinary Infections,* which summarizes the differences between these sulfonamides in the treatment of urinary infections, the evidence is presented that sulfacetamide is not the drug of choice in urinary infections, although it does belong in the group of effective drugs.

The superiority of the sulfonamides over other drugs is attributable not only to their bacteriostatic properties but also to their unique ability to permeate all the tissues and fluids of the body. Thus, they are effective in the parenchyma of organs, surrounding tissues, and mucous membranes.

The solubility of the sulfonamides in the urine is of importance, since renal complications are, in the main, due to the precipitation of the sulfonamides and their acetylated com-

pounds in the urine in one or another portion of the urinary system As a group they are relatively insoluble compounds, sulfathiazole and sulfadiazine especially so With the exception of sulfadiazine, the acetylated compounds are less soluble than the free sulfonamides The solubility of these substances is increased by alkalinization It has been stated that the effective concentration of sulfonamides in urine is close to 100 mg per 100 cc in *in vitro* experiments This is close to the limits of solubility of sulfadiazine and sulfathiazole in urine at pH 7 or 7 5 Bear in mind, therefore, that in attempting to achieve a particular concentration of these drugs in the urine, one may be approaching the point at which the sulfonamides precipitate out of solution and cause renal damage The urine, as well as being alkaline, must be adequate in volume if toxic renal effects are to be avoided Much used to be made of the point of concentrations of these drugs in the blood stream and urine I notice that the tendency now is to follow a fairly fixed schedule of dosage rather than to try to produce high levels of sulfonamide concentrations in the blood and in the urine Perhaps we shall hear more about the matter of desirable concentrations of the sulfonamides from other speakers

Mixtures of sulfonamides with mandelic acid and with methenamine are being promoted these days I know of no advantages which come from such mixtures Usually in such combinations, only one substance is present in amounts sufficient to produce any therapeutic effect

More recently the antibiotics have been added to the small group of drugs effective in urinary tract infections Penicillin, which has so many uses in infections in other systems of the body is very effective in gonorrhea, but other than this, its utility in urinary tract infections is highly limited

Streptomycin, as no doubt will be pointed out, has special applications in infections of the urinary tract It is more slowly eliminated than penicillin It is given in divided doses throughout the day by intramuscular injection, to maintain an

effective concentration in the body Streptomycin presents serious problems not present in the case of penicillin Bacteria develop resistance to it rather rapidly, in a period of days or weeks, so that if therapy is to be effective, the cure must be quickly achieved Streptomycin is not an innocuous drug It may cause allergic reactions such as rash or fever, it may produce serious renal damage, it may affect the blood forming organs, and it may cause a long lasting disturbance of the central nervous system with vertigo, tinnitus, and impaired hearing Such toxic effects are more apt to develop after the prolonged use of the drug and after large doses

In closing, perhaps I should mention the compound, phenothiazine, suggested as a urinary antiseptic, only to point out the hazards of new and insufficiently tested drugs It resembles methylene blue in many of its chemical characteristics It is effective as a urinary antiseptic, but in a series of 8 cases, 6 developed hemolytic anemia

Dr Wheeler Dr McLellan will continue the discussion

Dr Allister M McLellan The treatment of genitourinary tract infections has been revolutionized in the past ten years by the introduction of (1) a simple diagnostic procedure, namely, the excretory urogram, and (2) specific antimicrobial agents, namely, the sulfonamides, penicillin, and streptomycin

One cannot emphasize too strongly the importance of making careful diagnostic studies before treating infections in the genitourinary tract, since the infections may be the result of an abnormality which, in itself, is of greater importance to the patient than the pyuria

A careful physical examination may suggest specific pathologic conditions in the genitourinary tract Several examples may be cited Skin infections or boils may be the precursors of a perinephric abscess Abnormal neurologic conditions may be the cause of residual urine with its sequelae Abdominal examination may reveal an enlarged or tender kidney Psoas

spasm may mean a perinephric abscess A suprapubic mass is to be regarded as a full bladder until it is proved to be something else Inguinal gland enlargement may mean carcinoma or a primary lesion of the penis A scrotal sinus may be caused by tuberculosis of the epididymis Scrotal palpation may reveal early tuberculosis of the epididymis and testicular enlargement may be caused by such conditions as a teratoma or a gumma The prepuce should be retracted to examine the glans The meatus may be of pinhole size, causing serious back pressure Pus from the meatus should be examined with the Gram stain and cultured for gonococci Palpation of the urethra may reveal a periurethral abscess or tumor

The collection and prompt examination of all specimens of urine are most important The male patient should void in two glasses grossly visible pus in only the first glass indicates that it comes from the anterior urethra In the female, if a casual specimen is positive, a catheter specimen should be obtained to avoid contamination A specimen of urine for culture is obtained from the male by retracting the prepuce and washing off the glans penis As the patient continues to void, a specimen is collected in a sterile test tube in mid air,' as it were

Rectal examination will determine the anal sphincter tonicity and the mucous membrane changes in the canal itself The rectal mucosa is palpated routinely at this time Prostatic palpation will reveal the size shape and consistency of that organ, as well as irregularity, edema, and fluctuation An enlarged smooth rubbery gland means benign hypertrophy, a hard irregular gland may mean carcinoma tuberculosis or calculi, an edematous gland means inflammation, a fluctuating gland means an abscess Palpation of the seminal vesicles and base of the bladder should always be carried out and bimanual examination may be helpful when carcinoma or calculi are present in the bladder Prostatic secretion may be obtained for microscopic examination at this time if the condition is not acute

A plain X-ray and an intravenous pyelogram are simple benign procedures which give the physician a wealth of information. The plain X-ray may show an opaque stone, a large kidney (this is significant when its fellow is normal), or a soft shadow which may suggest perinephric abscess or residual urine in the bladder if the X-ray is taken after voiding. The intravenous pyelogram may indicate a relatively nonfunctioning kidney, but nevertheless, sufficient dye may be excreted to demonstrate obstruction and filling defects caused by stones, tumors, or blood clots. If all findings are normal with this procedure, the disease may be one which does not grossly disturb function or cause anatomic defects, for example, pyelitis or cystitis.

By a physical examination, simple laboratory tests, and excretory pyelogram a satisfactory working diagnosis may be made so that the patient can be intelligently handled. Cystoscopy is indicated for confirmation studies or biopsy, and occasionally for treatment.

The history of the treatment of urinary tract infection may be divided into three periods: (1) the preketogenic period, (2) the ketogenic period, and (3) the period of the sulfonamides and antibiotics.

1. The Preketogenic Period.—Prior to 1932, there were innumerable urinary antiseptics of which some colored the urine and some did not. Many caused digestive disturbances. I have been convinced from my own experience that the patient's recovery or improvement was often part of the natural course of the disease, rather than the result of treatment.

2. The Ketogenic Period.—The ketogenic diet was ushered in with the discovery that the urine of patients who suffered from ketosis had bacteriostatic properties. This was attributed to beta-hydroxy-butyric acid. Research along this line resulted in the discovery that mandelic acid had equal value. Later, calcium mandelate was introduced because it was less irritating to the gastrointestinal tract, and today, in this group, it is

the drug of choice Ambulatory patients tolerate it well, its unpleasant effects being limited to gastric discomforts The optimum dose of calcium mandelate is 2 Gm every 4 hours, a total of 12 Gm per day The output of the urine is limited to approximately 1,200 cc, which would give a concentration of about 1 per cent mandelic acid in the urine The pH of the urine should be 5 5 or less for the best results There is the danger of acidosis in cases with renal insufficiency, in infants, and in pregnancy This drug acts only in the excretory ducts of the urinary tract and, therefore, is effective only in the exudate on the mucous membrane, whereas the sulfonamide drugs are carried to the infecting agent deep in the tissues Calcium mandelate is a satisfactory urinary antiseptic for the more common uncomplicated urinary tract infections, but it has been largely replaced by more potent agents

3 The Sulfonamide and Antibiotic Period —In 1935, the discovery of sulfanilamide followed by its derivatives opened a new field in the therapy of infections of the urinary tract Of these drugs, sulfathiazole, sulfadiazine, and sulfamerazine have proved to be the most useful

Gonorrhea when treated with sulfathiazole or sulfadiazine, responds successfully to a dose of 1 Gm 4 times a day, with an equal amount of sodium bicarbonate for 7 days I should especially like to call your attention to the fact that no local treatment is indicated One may expect failure in about 5 per cent of cases of gonorrhea treated with sulfonamides The test of cure in these patients is by culture and stained smear of any secretion from the meatus first glass of voided urine, and prostatic secretion Cultures are made on chocolate agar grown under increased carbon dioxide tension

Today, however, penicillin is the drug of choice in the treatment of gonorrhea There are several satisfactory dosage plans The Marine Hospital on Staten Island has had a very large experience They found either one of these dosage schedules satisfactory first, a total of 200 000 units of penicillin in

saline given intramuscularly in divided doses over a period of 4 hours, each of the first 3 doses being 40,000 units and the final dose, 80,000 units; second, a single dose of 300,000 units in beeswax and oil. They treat the failures by doubling the dose, and they state that they have had no failures after 50,000 units every 2 hours for 40 doses.

Cases of non-specific urethritis do not respond well to sulfonamides. Non-tuberculous epididymitis and prostatitis do well with rest and may be helped with small doses of sulfathiazole or sulfadiazine. The cause of the disease should always be investigated.

A case of pyelitis or pyelonephritis always indicates the need for an intravenous pyelogram. Ureteral drainage may be indicated if the obstruction is in the ureter, and bladder drainage, if the obstruction is in the urethra or bladder neck. In these cases, a dose of 1 Gm. of a sulfonamide 4 times a day for 5 days rarely causes intoxication and almost invariably gives excellent results, when they are not complicated by obstructions, foreign bodies, or tumors.

Renal complications due to the sulfonamides clinically fall into two groups: (1) patients with a small amount of albumin, blood, and crystals in the urine; (2) patients in whom the drug crystallizes into conglomerated masses in the kidney tubules or pelvis, or ureter, giving rise to oliguria, nitrogen retention, and attacks of renal colic. The complication may be only unilateral. Both types are best handled by forcing fluids and alkalies, *and not by the immediate passage of catheters to both* kidneys. Cystoscopic treatment may be necessary in the second type, after judicial waiting. Since we now know that the crystals can form in the tubules of the kidneys themselves and cause anuria, passing a catheter up the ureter in these cases might do more harm than good.

Dr. Wheeler: I should like to ask Dr. Douglas to say a few words about this subject from the standpoint of the gynecologist.

Dr R Gordon Douglas The obstetrician or gynecologist is interested in urinary tract infections because of the frequency with which these complications are encountered in everyday practice The reasons for this are (1) The anatomic changes associated with pregnancy cause dilatation tortuosity increase in length and lateral displacement of the ureter (2) at least 80 per cent of pregnant patients have a tendency to develop a mild hydronephrosis The gynecologist also has to deal with urinary tract infections resulting from changes following the development of tumors surgical procedures and complications in the bladder after operative procedures

It is of a good deal of importance to us to know something about the normal status of the urinary tract from a bacteriologic point of view, prior to the onset of pregnancy My own experience indicates that the healthy urinary tract is free from organisms at all times It is of interest to note that Marple who studied the urinary tracts of a large number of women admitted to a medical service found 69 per cent of the cultures negative but in 19 per cent he found a bacilluria associated with pyuria and in an additional 10 per cent he found bacilluria alone Jaameri in Sweden analyzed the results of urine cultures of some 600 patients who were pregnant or in the early puerperium and found the colon aerogenes group of organisms present in some 16 per cent of the cases The experience of the latter investigator is quite in line with our own namely that in early pregnancy the urinary tract if it has previously been normal is sterile There is a tendency for bacilluria to develop as the physiologic hydronephrosis develops and it always in our experience precedes the development of pyuria

As Dr McLellan stated the early signs of pyuria are almost invariably asymptomatic By the time the patient develops clinical signs such as pain fever or chills we are usually dealing with a well advanced stage of the disease We are then confronted with the problem of treating an infection caused

saline given intramuscularly in divided doses over a period of 4 hours, each of the first 3 doses being 40,000 units and the final dose, 80,000 units, second, a single dose of 300,000 units in beeswax and oil They treat the failures by doubling the dose, and they state that they have had no failures after 50 000 units every 2 hours for 40 doses

Cases of non specific urethritis do not respond well to sulfonamides Non tuberculous epididymitis and prostatitis do well with rest and may be helped with small doses of sulfathiazole or sulfadiazine The cause of the disease should always be investigated

A case of pyelitis or pyelonephritis always indicates the need for an intravenous pyelogram Ureteral drainage may be indicated if the obstruction is in the ureter, and bladder drainage, if the obstruction is in the urethra or bladder neck In these cases, a dose of 1 Gm of a sulfonamide 4 times a day for 5 days rarely causes intoxication and almost invariably gives excellent results, when they are not complicated by obstructions, foreign bodies, or tumors

Renal complications due to the sulfonamides clinically fall into two groups (1) patients with a small amount of albumin, blood, and crystals in the urine, (2) patients in whom the drug crystallizes into conglomerated masses in the kidney tubules or pelvis or ureter, giving rise to oliguria, nitrogen retention, and attacks of renal colic The complication may be only unilateral Both types are best handled by forcing fluids and alkalies, and not by the immediate passage of catheters to both kidneys Cystoscopic treatment may be necessary in the second type, after judicial waiting Since we now know that the crystals can form in the tubules of the kidneys themselves and cause anuria passing a catheter up the ureter in these cases might do more harm than good

Dr Wheeler I should like to ask Dr Douglas to say a few words about this subject from the standpoint of the gynecologist.

Dr R Gordon Douglas The obstetrician or gynecologist is interested in urinary tract infections because of the frequency with which these complications are encountered in everyday practice The reasons for this are (1) The anatomic changes associated with pregnancy cause dilatation tortuosity increase in length and lateral displacement of the ureter (2) at least 80 per cent of pregnant patients have a tendency to develop a mild hydronephrosis The gynecologist also has to deal with urinary tract infections resulting from changes following the development of tumors surgical procedures and complications in the bladder after operative procedures

It is of a good deal of importance to us to know something about the normal status of the urinary tract from a bacteriologic point of view prior to the onset of pregnancy My own experience indicates that the healthy urinary tract is free from organisms at all times It is of interest to note that Marple who studied the urinary tracts of a large number of women admitted to a medical service found 69 per cent of the cultures negative but in 19 per cent he found a bacilluria associated with pyuria and in an additional 10 per cent he found bacilluria alone Jaameri in Sweden analyzed the results of urine cultures of some 600 patients who were pregnant or in the early puerperium and found the colon aerogenes group of organisms present in some 16 per cent of the cases The experience of the latter investigator is quite in line with our own namely that in early pregnancy the urinary tract if it has previously been normal is sterile There is a tendency for bacilluria to develop as the physiologic hydronephrosis develops and it always in our experience precedes the development of pyuria

As Dr McLellan stated the early signs of pyuria are almost invariably asymptomatic By the time the patient develops clinical signs such as pain fever or chills we are usually dealing with a well advanced stage of the disease We are then confronted with the problem of treating an infection caused

saline given intramuscularly in divided doses over a period of 4 hours, each of the first 3 doses being 40,000 units and the final dose, 80,000 units, second, a single dose of 300,000 units in beeswax and oil They treat the failures by doubling the dose, and they state that they have had no failures after 50 000 units every 2 hours for 40 doses

Cases of non specific urethritis do not respond well to sulfon amides Non tuberculous epididymitis and prostatitis do well with rest and may be helped with small doses of sulfathiazole or sulfadiazine The cause of the disease should always be in vestigated

A case of pyelitis or pyelonephritis always indicates the need for an intravenous pyelogram Ureteral drainage may be indi cated if the obstruction is in the ureter, and bladder drainage, if the obstruction is in the urethra or bladder neck In these cases, a dose of 1 Gm of a sulfonamide 4 times a day for 5 days rarely causes intoxication and almost invariably gives excel lent results, when they are not complicated by obstructions, foreign bodies, or tumors

Renal complications due to the sulfonamides clinically fall into two groups (1) patients with a small amount of albumin, blood, and crystals in the urine, (2) patients in whom the drug crystallizes into conglomerated masses in the kidney tubules or pelvis, or ureter, giving rise to oliguria, nitrogen retention, and attacks of renal colic The complication may be only uni lateral Both types are best handled by forcing fluids and alka lies, *and not by the immediate passage of catheters to* both kidneys Cystoscopic treatment may be necessary in the second type, after judicial waiting Since we now know that the crys tals can form in the tubules of the kidneys themselves and cause anuria, passing a catheter up the ureter in these cases might do more harm than good

Dr Wheeler I should like to ask Dr Douglas to say a few words about this subject from the standpoint of the gynecolo gist

Dr R Gordon Douglas The obstetrician or gynecologist is interested in urinary tract infections because of the frequency with which these complications are encountered in everyday practice The reasons for this are (1) The anatomic changes associated with pregnancy cause dilatation tortuosity increase in length and lateral displacement of the ureter (2) at least 80 per cent of pregnant patients have a tendency to develop a mild hydronephrosis The gynecologist also has to deal with urinary tract infections resulting from changes following the development of tumors surgical procedures and complications in the bladder after operative procedures

It is of a good deal of importance to us to know something about the normal status of the urinary tract from a bacteriologic point of view prior to the onset of pregnancy My own experience indicates that the healthy urinary tract is free from organisms at all times It is of interest to note that Marple who studied the urinary tracts of a large number of women admitted to a medical service found 69 per cent of the cultures negative but in 19 per cent he found a bacilluria associated with pyuria and in an additional 10 per cent he found bacilluria alone Jaameri in Sweden analyzed the results of urine cultures of some 600 patients who were pregnant or in the early puerperium and found the colon aerogenes group of organisms present in some 16 per cent of the cases The experience of the latter investigator is quite in line with our own namely that in early pregnancy the urinary tract if it has previously been normal is sterile There is a tendency for bacilluria to develop as the physiologic hydronephrosis develops and *it always in our experience precedes the development* of pyuria

As Dr McLellan stated the early signs of pyuria are almost invariably asymptomatic By the time the patient develops clinical signs such as pain fever or chills we are usually dealing with a well advanced stage of the disease We are then confronted with the problem of treating an infection caused

saline given intramuscularly in divided doses over a period of 4 hours, each of the first 3 doses being 40,000 units and the final dose, 80,000 units, second, a single dose of 300,000 units in beeswax and oil They treat the failures by *doubling the* dose, and they state that they have had no failures after 50 000 units every 2 hours for 40 doses

Cases of non specific urethritis do not respond well to sulfonamides Non tuberculous epididymitis and prostatitis do well with rest and may be helped with small doses of sulfathiazole or sulfadiazine The cause of the disease should always be investigated

A case of pyelitis or pyelonephritis always indicates the need for an intravenous pyelogram Ureteral drainage may be indicated if the obstruction is in the ureter, and bladder drainage, if the obstruction is in the urethra or bladder neck In these cases, a dose of 1 Gm of a sulfonamide 4 times a day for 5 days rarely causes intoxication and almost invariably gives excellent results, when they are not complicated by obstructions, foreign bodies, or tumors

Renal complications due to the sulfonamides clinically fall into two groups (1) patients with a small amount of albumin, blood, and crystals in the urine, (2) patients in whom the drug crystallizes into conglomerated masses in the kidney tubules or pelvis, or ureter, giving rise to oliguria, nitrogen retention and attacks of renal colic The complication may be only unilateral Both types are best handled by forcing fluids and alkalies, and not by the immediate passage of catheters to both kidneys Cystoscopic treatment may be necessary in the second type, after judicial waiting Since we now *know that the* crystals can form in the tubules of the kidneys themselves and cause anuria, passing a catheter up the ureter in these cases might do more harm than good

Dr Wheeler I should like to ask Dr Douglas to say a few words about this subject from the standpoint of the gynecologist

Dr R Gordon Douglas The obstetrician or gynecologist is interested in urinary tract infections because of the frequency with which these complications are encountered in everyday practice The reasons for this are (1) The anatomic changes associated with pregnancy cause dilatation tortuosity increase in length and lateral displacement of the ureter (2) at least 80 per cent of pregnant patients have a tendency to develop a mild hydronephrosis The gynecologist also has to deal with urinary tract infections resulting from changes following the development of tumors surgical procedures and complications in the bladder after operative procedures

It is of a good deal of importance to us to know something about the normal status of the urinary tract from a bacteriologic point of view prior to the onset of pregnancy My own experience indicates that the healthy urinary tract is free from organisms at all times It is of interest to note that Marple who studied the urinary tracts of a large number of women admitted to a medical service found 69 per cent of the cultures negative but in 19 per cent he found a bacilluria associated with pyuria and in an additional 10 per cent he found bacilluria alone Jaameri in Sweden analyzed the results of urine cultures of some 600 patients who were pregnant or in the early puerperium and found the colon aerogenes group of organisms present in some 16 per cent of the cases The experience of the latter investigator is quite in line with our own namely that in early pregnancy the urinary tract if it has previously been normal is sterile There is a tendency for bacilluria to develop as the physiologic hydronephrosis develops and it always in our experience precedes the development of pyuria

As Dr McLellan stated the early signs of pyuria are almost invariably asymptomatic By the time the patient develops clinical signs such as pain fever or chills we are usually dealing with a well advanced stage of the disease We are then confronted with the problem of treating an infection caused

by a temporary physiologic abnormality The treatment is usually directed toward the infection rather than the anatomic changes

Our experience with antimicrobial agents indicates that they are all ineffective with the exception of mandelic acid the sulfonamide drugs, penicillin, and streptomycin The sulfonamide drugs which we have employed have been limited largely to 3 compounds sulfanilamide, sulfathiazole, and sulfadiazine I used sulfacetamide when it was first introduced, and, in my experience, the value of that drug has been comparable to that of sulfanilamide

Formerly, when we employed sulfanilamide it was our custom to restrict fluids during the administration of the drug in order to keep the urinary output below 1,000 cc We have altered this practice in the employment of sulfathiazole and sulfadiazine, and we make every effort to maintain a daily urinary output of at least 1,500 cc By adherence to this technic we have not encountered any of the serious renal complications such as hematuria or renal colic, that have been so frequently reported by others Furthermore, in a patient who has rather poor renal function, we reduce the dose, since in such a case, it may take only one half of the dosage to obtain the same results It used to be our practice to determine the concentration of the drug in both the urine and the blood at frequent intervals but further experience has shown that these concentrations bear no relation to the therapeutic results The latter depend more on the nature of the infecting organism and the duration and extent of the pathologic process

Two brief case histories may serve to illustrate some of our results A young woman 19 years of age who has been in the Woman s Clinic for the past month gave a history of mild urinary tract infections at the ages of 3 5 6 and 15 years This patient was entirely asymptomatic and afebrile throughout her pregnancy Intravenous pyelograms revealed a bilateral

pyelonephritis more marked on the left side with greatly distended renal pelves and ureters The disease was detected because of pyuria The causative organism Bacillus aerogenes disappeared following sulfathiazole therapy but a streptococcus remained Despite the extensive involvement the patient had no symptoms There is one difficulty in interpreting the results Infections in our cases are almost invariably (93 per cent) caused by one of the members of the colon aerogenes group of organisms After the administration of a sulfonamide in the great majority of instances one can eliminate at least temporarily the causative organism from the urinary tract but in our experience it has been very common particularly in the patient who has a chronic infection to find a nonhemolytic type of streptococcus and in some instances an anaerobic streptococcus as a residual chronic invader of the urinary tract. This was true in the case history just cited I don t know the significance of the presence of these organisms I look upon them as secondary invaders such as one might find in wound infection That may or may not be correct As long as these organisms are found on culture it seems to me that we are not positive that the urinary tract infection in question has been eliminated As far as I am aware most of the clinical reports in this country have not referred to this particular problem

Let me present a historical review of another patient with a chronic infection seen in our clinic She was treated with a ketogenic diet mandelic acid pelvic lavage cystoscopy and sulfonamides There were positive cultures practically throughout the entire period of 6 years A negative culture was obtained for the first time after the administration of sulfanilamide and negative cultures were obtained on several occasions after sulfadiazine When this patient was seen in the Out Patient Department one week ago a positive culture was again obtained This indicates how ineffectual are urinary antiseptics in patients with chronic pyelonephritis

by a temporary physiologic abnormality The treatment is usually directed toward the infection rather than the anatomic changes

Our experience with antimicrobial agents indicates that they are all ineffective with the exception of mandelic acid, the sulfonamide drugs, penicillin, and streptomycin The sulfonamide drugs which we have employed have been limited largely to 3 compounds sulfanilamide, sulfathiazole, and sulfadiazine I used sulfacetamide when it was first introduced, and, in my experience, the value of that drug has been comparable to that of sulfanilamide

Formerly, when we employed sulfanilamide, it was our custom to restrict fluids during the administration of the drug in order to keep the urinary output below 1,000 cc We have altered this practice in the employment of sulfathiazole and sulfadiazine, and we make every effort to maintain a daily urinary output of at least 1,500 cc By adherence to this technic we have not encountered any of the serious renal complications, such as hematuria or renal colic, that have been so frequently reported by others Furthermore, in a patient who has rather poor renal function, we reduce the dose, since in such a case, it may take only one half of the dosage to obtain the same results It used to be our practice to determine the concentration of the drug in both the urine and the blood at frequent intervals, but further experience has shown that these concentrations bear no relation to the therapeutic results The latter depend more on the nature of the infecting organism and the duration and extent of the pathologic process

Two brief case histories may serve to illustrate some of our results A young woman, 19 years of age, who has been in the Woman s Clinic for the past month, gave a history of mild urinary tract infections at the ages of 3, 5, 6 and 15 years This patient was entirely asymptomatic and afebrile throughout her pregnancy Intravenous pyelograms revealed a bilateral

were made on 30 girls and young women who had been treated for urinary infections in the Harriet Lane Home in Baltimore Among these, 21 had a history of more than 1 episode of urinary tract infection, and in these, 10 showed abnormalities of the urinary tract in an average of 10 years after their infection, as demonstrated by the urogram in most cases In others, abnormalities were found in the urine Among these youngsters, 9 had a history of only 1 attack of infection, and although some 13 years elapsed after the supposedly single attack, 6 of the 9 still showed urinary abnormalities The chronicity and difficulty of clearing up urinary tract infections in the age group which we treat constitute one aspect of the problem There are two other reasons why these infections are important to us They are frequent, and they occasionally prove fatal I am now referring to non tuberculous and non-gonorrheal infections involving the kidneys, ureters, bladder, or a combination of these In pediatrics, we encounter 2 general types In one group, the pathology is confined to the kidney; there are many fine abscesses throughout the kidney, and, in about 5 per cent of the cases, a very slight degree of pyelitis is present, there is no obstruction of the urinary tract This type occurs chiefly in children under 3 years of age and is usually caused by the colon bacillus The course is usually brief The symptomatology is scant in many cases, the children suffering primarily from a disease of another system, although some of these cases are seriously ill In the second group the infection occurs in the kidney, ureter, bladder, or in combinations of these These children are usually older There is frequently more than one organism The course is chronic There is a tendency to recurrence after apparent cure, and many go on to develop pyelonephritis and other complications

In a youngster with urinary tract infection if we assume that the diagnosis has been correctly made and the pus in the urine has been correctly interpreted, our procedure is as follows We obtain a culture of the urine, and if the patient s condition per-

I might mention the results of an analysis I made of a small group of our patients In the first culture of a group of antepartum patients, 30 had the E coli, 1 had the B aerogenes and only 1 had the Staphylococcus aureus In the first culture of a group of postpartum patients, 47 had the E coli and 7 had the B aerogenes This relationship is what we see in our routine practice year in and year out In the last cultures of the antepartum group, the colon bacillus was present in 1, and the B aerogenes in 2 In the last culture of the postpartum group, the colon bacillus was present in 12, and the B aerogenes in 2 The Staphylococcus albus and the nonhemolytic streptococcus were present relatively frequently in the postpartum group Diphtheroids were occasionally found The Staphylococcus aureus was eliminated Only one half of the patients had absolutely sterile urine when last seen

If we look at the problem in another way, from the stand point of elimination of the causative organism which is the usual method of reporting the results in the literature, and relate our results to the drug employed, we find that in the antepartum group, where sulfanilamide was employed the causative organism was eliminated in 11 patients and was still present in 10 In the postpartum group, with the same drug, the organism was eliminated in 20 patients and was still present in 14 With sulfadiazine and sulfathiazole, however, the causative organism was eliminated in all but 1 patient during the course of therapy

If the index of cure is based solely on the microscopic examination of the sediment of the urine, we will frequently overlook streptococci or other organisms present in small numbers Pyuria may persist where the colon aerogenes infection has been eliminated, and only a nonhemolytic streptococcus found on culture

Dr Wheeler Dr Glynn, how does the pediatrician face the problem of urinary tract infections?

Dr Martin J Glynn In 1937, some follow up observations

who, either in infancy or childhood, have had more than one episode of urinary tract infection.

Dr. Wheeler: We would like now to have some discussion by members of the audience. Do you have questions that you would like to ask the participants?

Student: What percentage of urinary infections would clear up by themselves, without any treatment at all?

Dr. McLellan: In cases not complicated by structural defects or obstructions, I would expect practically 100 per cent to clear up spontaneously; in the complicated cases, if the infection did clear up, I would expect it to return.

Dr. Modell: Dr. Douglas stated that sulfanilamide is less effective than sulfadiazine and sulfathiazole. Is there any preference between the latter two?

Dr. Wheeler: Dr. Douglas, from your experience, which is the drug of choice?

Dr. Douglas: As far as I can tell from the information available, there is practically no difference between sulfathiazole and sulfadiazine in the matter of therapeutic effectiveness. However, in my own experience, sulfadiazine has caused the patients fewer distressing symptoms.

Dr. Wheeler: What about your experience, Dr. McLellan?

Dr. McLellan: I have had excellent results in 95 per cent of my cases of gonorrhea treated with either sulfathiazole or sulfadiazine, but 90 per cent of this experience has been with sulfathiazole. If one drug failed to cure the patient, the other also failed. Now, however, we treat all cases of gonorrhea with penicillin.

Student: If the sulfadiazine works mostly behind the kidney epithelium, is it necessary to put a restriction on the maximum amount of urine?

Dr. McLellan: The output of urine should be at least 2,000 cc. daily to protect the kidneys against crystal formation. I see no objection to its being doubled. The concentration of the

mits more than one culture to discover the type of organism before therapy is started In many cases however, we cannot wait for the result of the culture, or even wait to take more than one preliminary specimen Supportive treatment is of great importance in these infants If the subject is under 2 years of age and has not had a previous history of a urinary tract infection, pyelograms, excretory or retrograde, are not necessary In the event, however, that the youngster is more than 3 years old, or has had a previous episode, the intravenous pyelogram is indicated, and should its interpretation be open to doubt, a retrograde pyelogram should be made

The acute pyurias in the age group which we treat are due to the colon bacillus in 80 per cent of the cases with or without the B pyocyaneus or B proteus The S faecalis is also a common offender in our group Sulfadiazine and sulfathiazole are the drugs of choice if the child needs treatment before we receive the report of the culture If we can wait for the report of the culture before treatment is started, and the organism proves to be the S faecalis calcium mandelate is probably still the best drug The dosage of the mandelate aims to produce a concentration of from 0 5 to 1 per cent in the urine, or about 1 Gm per 100 cc of urine, given in 4 doses throughout the day In the case of the sulfonamide, for an infant, I would begin with 0 2 Gm per Kg per day divided into 4 or 6 doses. The examination of the urine and the concentration of the drug in the blood are used as guides for adjusting the dosage In a few days, it may be necessary to reduce the dose to 0 1 Gm per Kg daily divided into 4 or 6 fractions

In pyocyaneus infections we find a difficult problem on our hands For such cases, unfortunately, I cannot recommend any agent in which I have any confidence although our resident, Dr Miller, states that his results with streptomycin have been similar to those reported in the literature

May I stress again the need for urologic studies in children

who, either in infancy or childhood, have had more than one episode of urinary tract infection

Dr Wheeler. We would like now to have some discussion by members of the audience Do you have questions that you would like to ask the participants?

Student What percentage of urinary infections would clear up by themselves, without any treatment at all?

Dr McLellan In cases not complicated by structural defects or obstructions, I would expect practically 100 per cent to clear up spontaneously, in the complicated cases, if the infection did clear up, I would expect it to return

Dr Modell Dr Douglas stated that sulfanilamide is less effective than sulfadiazine and sulfathiazole Is there any preference between the latter two?

Dr Wheeler Dr Douglas, from your experience, which is the drug of choice?

Dr Douglas As far as I can tell from the information available, there is practically no difference between sulfathiazole and sulfadiazine in the matter of therapeutic effectiveness. However, in my own experience, sulfadiazine has caused the patients fewer distressing symptoms

Dr Wheeler What about your experience Dr McLellan?

Dr McLellan I have had excellent results in 95 per cent of my cases of gonorrhea treated with either sulfathiazole or sulfadiazine, but 90 per cent of this experience has been with sulfathiazole If one drug failed to cure the patient, the other also failed Now, however, we treat all cases of gonorrhea with penicillin

Student If the sulfadiazine works mostly behind the kidney epithelium, is it necessary to put a restriction on the maximum amount of urine?

Dr McLellan The output of urine should be at least 2 000 cc daily to protect the kidneys against crystal formation I see no objection to its being doubled The concentration of the

drug in the blood and tissues is far more important than that in the urine.

Dr. Wheeler: Do your results depend on the type of infecting organism?

Dr. McLellan: In the uncomplicated cases, in the absence of a tumor, retention of urine, or a stone, our results with sulfonamides are good in all common types of infections except those produced by the nonhemolytic streptococcus, B. aerogenes, B. proteus, and B. pyocyaneus. The sulfonamides have no effect on tubercule bacilli in the urinary tract.

Dr. Harry Gold: Do bacteria in urinary tract infections respond differently to the sulfonamides from similar bacteria in other organs of the body?

Dr. Walsh McDermott: I may have something to report on that, Dr. Gold. The Streptococcus viridans which we have been finding in the urines of patients on Dr. McLellan's and Dr. Marshall's urological service is, in many cases, resistant to *in vitro* concentrations of 10 mg. of sulfadiazine per 100 cc., whereas the Streptococcus viridans which we find in the blood of patients with subacute bacterial endocarditis is not resistant to the drug.

Dr. Gold: Have you encountered any case that developed resistance to one of the sulfonamides and then was cured by another? This relates to the question of shifting from one preparation to another if matters don't go well with the first.

Dr. Douglas: I have a case in point. A patient received sulfanilamide for a period of 6 days, a daily dosage of 5.4 Gm., without therapeutic effect. She responded promptly, within a period of days, when sulfadiazine was administered following an interval of 2 days without medication. I have had other comparable experiences. Sulfathiazole and sulfadiazine are more effective drugs than sulfanilamide.

Dr. McKeen Cattell: I take it that those cases throw no light on the question of acquired drug-fastness.

Dr Douglas I don't believe so It might be well to note the fact that in an infection with extensive pyuria, an inhibitor such as para amino-benzoic acid is present in the urine and this diminishes the efficacy of the sulfonamides If there are focal abscesses in the urinary tract, the therapeutic response is poor or delayed I do not believe that our experience necessarily indicates that the organism has become drug fast

Dr Modell It is accepted that sulfadiazine and sulfathiazole are approximately equally effective in urinary infections Do you know of cases in which one of these two was not effective and the other was?

Dr Douglas I know of instances in which, after the lapse of time there was response to one drug although there had been no response to the other I do not believe, however, that that quite answers your question

Dr Wheeler Dr Cattell, would you say a word about the pyridium sulfonamide combination? It introduces a new point

Dr Cattell That has been a subject of recent interest, arising from the observations of Neter who noted in test tube experiments that a combination of pyridium with the sulfonamides both at subeffective concentrations, will destroy the organism Incidentally, it should be mentioned that the toxicity of sulfadiazine is decreased by the simultaneous administration of pyridium and the question arises as to whether that combination might not be useful in urinary infections I think Dr McDermott has firsthand knowledge on that point

Dr McDermott We repeated Neter s work, and in the test tube with E coli, a small amount of sulfadiazine given with pyridium proved more effective than that amount of sulfadiazine alone That also holds true for pneumococcus type I. However, this has not been borne out for pneumococcus type I infection in mice In other words *in vivo* we have not found this synergism, nor so far, in the patients whom we have studied with Dr McLellan

Dr. Modell: Pyridium has practically no bacteriostatic properties in the test tube.

Dr. McDermott: Very little, according to the studies which we have made.

Dr. Wheeler: If one looks through the charts from the urology service, one notes that most patients nowadays who have an operation for benign hypertrophy of the prostate receive sulfadiazine or sulfathiazole prophylactically. Has that proved to be a worth-while procedure?

Dr. McLellan: It should not be given routinely. I think the drug should be given if the urinary tract is badly infected before the operation, along with adequate catheter drainage as indicated. I think the drug is given entirely too often both before and after operation.

Dr. Wheeler: The urology service now also gives the patients sulfaguanidine or sulfasuccidine before implantation of the ureters in the bowel. Has that proved worth while?

Dr. McLellan: All the patients have done extremely well, but I attribute the success to the surgical skill of the resident urologist. No drug will ever make up for incompetent surgery.

Dr. Wheeler: Dr. Barr, do you have any comment?

Dr. David P. Barr: I should like to ask Dr. McLellan about the treatment of the "gleet," chronic gonorrhea.

Dr. McLellan: A patient, complaining of "gleet" when first seen, should be examined by smear and culture to determine whether or not he has gonorrhea. If gonococci are present, good results can be anticipated with the sulfa drugs or penicillin. If it is a case of non-specific urethritis, these drugs are disappointing. The principal causes of non-specific urethritis are poor sexual hygiene and stricture of the urethra, in the presence of chronic prostatitis. Prostatitis is promoted and aggravated by ungratified sexual excitement and by prolonging the sexual act. Most cases of prostatitis give no history of gonorrhea. Stricture of the urethra with associated prostatitis will clear up with dilatation of the stricture. The prognosis is good in non-

specific urethritis, and in the absence of stricture a spontaneous recovery is assured. Most important in "gleet" cases is the physician's competency to determine whether or not the patient has a contagious disease. This group of patients is very much overtreated. Massaging the prostate, bladder irrigations, and sound treatments are carried to a ridiculous degree, in my opinion. I rarely rub a prostate for therapeutic purposes.

Dr. Barr: In those cases do you find any predominant group of organisms?

Dr. McLellan: It is invariably a mixed infection.

Dr. Barr: And you feel there is no utility in the drugs in those cases?

Dr. McLellan: I feel that the drug is of little value in a case of non-specific urethritis.

Dr. Wheeler: Most general practitioners, including the ones who used to send the cases of "clap" to the urologist, now treat these cases themselves with sulfonamides or penicillin. Is that permissible?

Dr. McLellan: Any physician can treat simple gonorrhea, provided he is qualified to make a diagnosis, to administer antimicrobial agents, and to make a test of cure, which means a smear and culture.

Dr. Wheeler: You do not pass sounds?

Dr. McLellan: I do not pass sounds and do not massage prostates.

Dr. Wheeler: Should the general practitioner treat a gonococcal urethritis in a female?

Dr. Douglas: In the female, of course, gonorrhea involves not only the urinary but the genital tract. I think Dr. McLellan has answered that question. Any person who has the ability to make the diagnosis can determine the cure, and anyone who has sufficient knowledge to direct the chemotherapy can adequately care for these patients. The practitioner not prepared to take cultures will miss the diagnosis of gonorrhea very frequently, since in gonorrhea, the culture is positive twice as

often as the smear, while of those with negative culture, only 2 or 3 per cent exhibit a positive smear

In my opinion, the drugs seem to be a little more effective in the female than in the male Recently I reported on a group of nearly 200 patients in whom the average time for cure with sulfadiazine (cultures were taken every 2 hours) was 9 to 12 hours In one experimental group we gave only 8 Gm of the drug in 2 doses over a period of 4 hours, with satisfactory results

Dr Cattell If I understand the position of the urologist correctly, he attributes no part of the curative action of the sulfonamide to a local action in the lumen of the urinary tract. The volume of urine and the pH of the urine would hardly be expected to play a part, if we are to attribute the curative action to the concentration in the tissues Is that your view?

Dr McLellan Yes, I believe that the action is due to the concentration in the blood and tissues and not in the urine

Dr Gold Would you state to what extent you depend on the drug blood levels as a guide to dosage? Do you adopt a routine plan of dosage and simply pursue it until the patient is cured, or do you determine blood levels and aim to attain a particular level as a means of insuring a cure?

Dr Douglas Our practice is to start the average patient with a dosage of 6 Gm per day and to continue the medication for not longer than 6 days If a therapeutic effect is not obtained within 6 days I do not believe it does any good to continue longer I think the dangers of toxic effects can be greatly reduced if one does not prolong the administration beyond 6 days We determine concentrations in the blood and urine every second day and, in some instances, daily It is not necessary in the average patient, but in the patient with impaired renal function, this information is valuable to prevent toxicity

Dr Cattell But you do not use it in connection with the adjustment of dosage for the therapeutic action?

Dr Douglas No

Dr Barr Helmholtz has emphasized that very small amounts of sulfonamides may be effective in pyelitis Have you had any experience with small amounts that is have doses of less than 1 Gm a day an effect?

Dr Douglas I think it is interesting in connection with Dr Barr s remark that Kenny who was associated with Colebrook at the time the original work was done at the Queen Charlotte s Hospital advocated 0 5 Gm of sulfanilamide 3 times a day That would be 1 5 Gm per day That may be effective in a very mild type of urinary tract infection one that involves little or no pathologic or anatomic change Helmholtz is quite correct in the statement that small doses have an antibacterial effect. He advocated 0 5 Gm a day but that is entirely ineffective in a patient who has anything approaching a serious urinary tract infection In our experience the dosage employed and advocated by Kenny was entirely ineffective

In answering another question that came up a little earlier, I might state that Crabtree in Boston has reported spontaneous cures in 65 per cent of women who have had definite febrile phases of urinary tract infection in pregnancy This fits in exactly with our own experience of the presulfonamide days Spontaneous cures often occur but as Dr McLellan said if there is a residual urine or an abnormal urinary tract such cures do not usually take place at the end of 4 months In my opinion Kenny was including a number of spontaneous cures

Perhaps it would be well if I summarized my views Sulfadiazine in divided doses of 4 to 6 Gm daily is the drug of choice in the treatment of the usual type of urinary tract infection encountered in obstetrical and gynecological patients Somewhat smaller doses 2 to 4 Gm may be employed for prophylactic reasons or in the treatment of very mild infections Penicillin is of very little value in the treatment of the infections commonly encountered because these are usually

due to gram-negative bacilli. It may be of value occasionally in infections by gram-positive cocci, in conjunction with sulfadiazine where the latter drug has not controlled the infection. It may also be of value on rare occasions in eradicating secondary invaders, previously referred to, where they appear to be responsible for maintaining a chronic inflammation.

Since the response to sulfadiazine has been relatively prompt and satisfactory, and since renal toxicity has been practically eliminated by maintaining the pH of the urine at 7 or above, there has been little incentive to experiment with streptomycin. This compound is both expensive and toxic. Recent experience indicates that the former dosages of 2 to 4 Gm. are not necessary, and that equally satisfactory results can be obtained with from 1 to 1.5 Gm. per day given intramuscularly in divided doses. We have observed the results with streptomycin in a limited number of urinary tract infections where the primary indication was tuberculosis or serious pelvic infection. In these experiences, the results have been satisfactory but, except for tuberculosis, they are in no way superior to those obtained with sulfadiazine, and I feel that in the light of our present knowledge, streptomycin should only be used in the rare instances where sulfadiazine fails.

In the treatment of gonorrhea, penicillin has largely replaced sulfadiazine because of its even more spectacular results. Various dosage schedules such as 20,000 to 30,000 units every 2 to 3 hours for 5 doses have given almost uniformly satisfactory results. More recently we have used a single intramuscular injection of 300,000 units in saline with equally good results. We prefer this latter method to the beeswax-oil preparation which has a disadvantage in the vehicle employed. Frequent culture studies are still of the greatest importance in following the course in this field.

Dr. Gold: In relation to the toxicity of combinations of the sulfonamides, attention might be called to the observation that one sulfonamide in a saturated solution will not precipitate

out if another sulfonamide is added to that solution In consequence of this fact a quantity of sulfonamides composed of 3 members of the group will make a solution with less hazard of precipitation than a similar quantity composed of only 1 sulfonamide There is a preparation on the market composed of equal parts of sulfadiazine sulfamerazine and sulfathiazole and there is some indication from observations in man that such a combination provides the therapeutic effects of the sum of the 3 but the hazard of precipitation of crystals in urine is only that of 1 of the ingredients of the mixture While there are indications that such a mixture might be advantageous there is need for more clinical experience to be sure that such a mixture is superior to any one compound alone

Dr Wheeler Dr Marshall I wonder if we could have your reaction to the views that have been expressed in regard to the technics and drugs employed in the treatment of genitourinary infections on the urological service

Dr Victor F Marshall In general I am in agreement with what has already been said Except for gonorrhea and tuberculosis infections of the urinary tract in the male are usually associated with obstruction or a tumor or a foreign body These must be properly treated before the infection can be eradicated. The sulfa drugs seem to be particularly useful in the streptococcal infections and penicillin in the staphylococcal infections There are a few organisms which are still extremely difficult to manage In adult male urology we have the same trouble with the B pyocyaneus as Dr Glynn has in pediatric practice We have tried streptomycin and in our limited experience we have had very little success I remember one patient specifically to whom the drug was given parenterally and also through the nephrostomy following the removal of a stone and even such intensive streptomycin therapy failed to eliminate the B pyocyaneus The B proteus is another common and very tenacious infection in the urinary tract. It is particularly objectionable because it is a vigorous

due to gram-negative bacilli. It may be of value occasionally in infections by gram-positive cocci, in conjunction with sulfadiazine where the latter drug has not controlled the infection. It may also be of value on rare occasions in eradicating secondary invaders, previously referred to, where they appear to be responsible for maintaining a chronic inflammation.

Since the response to sulfadiazine has been relatively prompt and satisfactory, and since renal toxicity has been practically eliminated by maintaining the pH of the urine at 7 or above, there has been little incentive to experiment with streptomycin. This compound is both expensive and toxic. Recent experience indicates that the former dosages of 2 to 4 Gm. are not necessary, and that equally satisfactory results can be obtained with from 1 to 1.5 Gm. per day given intramuscularly in divided doses. We have observed the results with streptomycin in a limited number of urinary tract infections where the primary indication was tuberculosis or serious pelvic infection. In these experiences, the results have been satisfactory but, except for tuberculosis, they are in no way superior to those obtained with sulfadiazine, and I feel that in the light of our present knowledge, streptomycin should only be used in the rare instances where sulfadiazine fails.

In the treatment of gonorrhea, penicillin has largely replaced sulfadiazine because of its even more spectacular results. Various dosage schedules such as 20,000 to 30,000 units every 2 to 3 hours for 5 doses have given almost uniformly satisfactory results. More recently we have used a single intramuscular injection of 300,000 units in saline with equally good results. We prefer this latter method to the beeswax-oil preparation which has a disadvantage in the vehicle employed. Frequent culture studies are still of the greatest importance in following the course in this field.

Dr. Gold: In relation to the toxicity of combinations of the sulfonamides, attention might be called to the observation that one sulfonamide in a saturated solution will not precipitate

out if another sulfonamide is added to that solution In consequence of this fact, a quantity of sulfonamides composed of 3 members of the group will make a solution with less hazard of precipitation than a similar quantity composed of only 1 sulfonamide There is a preparation on the market composed of equal parts of sulfadiazine, sulfamerazine, and sulfathiazole, and there is some indication from observations in man that such a combination provides the therapeutic effects of the sum of the 3, but the hazard of precipitation of crystals in urine is only that of 1 of the ingredients of the mixture While there are indications that such a mixture might be advantageous, there is need for more clinical experience to be sure that such a mixture is superior to any one compound alone

Dr Wheeler Dr Marshall, I wonder if we could have your reaction to the views that have been expressed in regard to the technics and drugs employed in the treatment of genitourinary infections on the urological service

Dr Victor F Marshall In general I am in agreement with what has already been said Except for gonorrhea and tuber culosis infections of the urinary tract in the male are usually associated with obstruction, or a tumor, or a foreign body These must be properly treated before the infection can be eradicated The sulfa drugs seem to be particularly useful in the streptococcal infections, and penicillin in the staphylococcal infections There are a few organisms which are still ex tremely difficult to manage In adult male urology, we have the same trouble with the B pyocyaneus as Dr Glynn has in pediatric practice We have tried streptomycin and in our limited experience, we have had very little success I remem ber one patient specifically to whom the drug was given par enterally and also through the nephrostomy following the re moval of a stone, and even such intensive streptomycin therapy failed to eliminate the B pyocyaneus The B proteus is an other common and very tenacious infection in the urinary tract. It is particularly objectionable because it is a vigorous

due to gram-negative bacilli. It may be of value occasionally in infections by gram-positive cocci, in conjunction with sulfadiazine where the latter drug has not controlled the infection. It may also be of value on rare occasions in eradicating secondary invaders, previously referred to, where they appear to be responsible for maintaining a chronic inflammation.

Since the response to sulfadiazine has been relatively prompt and satisfactory, and since renal toxicity has been practically eliminated by maintaining the pH of the urine at 7 or above, there has been little incentive to experiment with streptomycin. This compound is both expensive and toxic. Recent experience indicates that the former dosages of 2 to 4 Gm. are not necessary, and that equally satisfactory results can be obtained with from 1 to 1.5 Gm. per day given intramuscularly in divided doses. We have observed the results with streptomycin in a limited number of urinary tract infections where the primary indication was tuberculosis or serious pelvic infection. In these experiences, the results have been satisfactory but, except for tuberculosis, they are in no way superior to those obtained with sulfadiazine, and I feel that in the light of our present knowledge, streptomycin should only be used in the rare instances where sulfadiazine fails.

In the treatment of gonorrhea, penicillin has largely replaced sulfadiazine because of its even more spectacular results. Various dosage schedules such as 20,000 to 30,000 units every 2 to 3 hours for 5 doses have given almost uniformly satisfactory results. More recently we have used a single intramuscular injection of 300,000 units in saline with equally good results. We prefer this latter method to the beeswax-oil preparation which has a disadvantage in the vehicle employed. Frequent culture studies are still of the greatest importance in following the course in this field.

Dr. Gold: In relation to the toxicity of combinations of the sulfonamides, attention might be called to the observation that one sulfonamide in a saturated solution will not precipitate

out if another sulfonamide is added to that solution In conse quence of this fact a quantity of sulfonamides composed of 3 members of the group will make a solution with less hazard of precipitation than a similar quantity composed of only 1 sul fonamide *There is a preparation on the market composed of* equal parts of sulfadiazine sulfamerazine and sulfathiazole and there is some indication from observations in man that such a combination provides the therapeutic effects of the sum of the 3 but the hazard of precipitation of crystals in urine is only that of 1 of the ingredients of the mixture While there are indications that such a mixture might be advantageous there is need for more clinical experience to be sure that such a mixture is superior to any one compound alone

Dr Wheeler Dr Marshall I wonder if we could have your reaction to the views that have been expressed in regard to the technics and drugs employed in the treatment of genitourinary infections on the urological service

Dr Victor F Marshall In general I am in agreement with what has already been said Except for gonorrhea and tuber culosis infections of the urinary tract in the male are usually associated with obstruction or a tumor or a foreign body These must be properly treated before the infection can be eradicated. The sulfa drugs seem to be particularly useful in the streptococcal infections and penicillin in the staphylococ cal infections There are a few organisms which are still ex tremely difficult to manage In adult male urology we have the same trouble with the B pyocyaneus as Dr Glynn has in pediatric practice We have tried streptomycin and in our limited experience we have had very little success *I remem* ber one patient specifically to whom the drug was given par enterally and also through the nephrostomy following the re moval of a stone and even such intensive streptomycin therapy failed to eliminate the B pyocyaneus The B proteus is an other common and very tenacious infection in the urinary tract. It is particularly objectionable because it is a vigorous

due to gram-negative bacilli. It may be of value occasionally in infections by gram-positive cocci, in conjunction with sulfadiazine where the latter drug has not controlled the infection. It may also be of value on rare occasions in eradicating secondary invaders, previously referred to, where they appear to be responsible for maintaining a chronic inflammation.

Since the response to sulfadiazine has been relatively prompt and satisfactory, and since renal toxicity has been practically eliminated by maintaining the pH of the urine at 7 or above, there has been little incentive to experiment with streptomycin. This compound is both expensive and toxic. Recent experience indicates that the former dosages of 2 to 4 Gm. are not necessary, and that equally satisfactory results can be obtained with from 1 to 1.5 Gm. per day given intramuscularly in divided doses. We have observed the results with streptomycin in a limited number of urinary tract infections where the primary indication was tuberculosis or serious pelvic infection. In these experiences, the results have been satisfactory but, except for tuberculosis, they are in no way superior to those obtained with sulfadiazine, and I feel that in the light of our present knowledge, streptomycin should only be used in the rare instances where sulfadiazine fails.

In the treatment of gonorrhea, penicillin has largely replaced sulfadiazine because of its even more spectacular results. Various dosage schedules such as 20,000 to 30,000 units every 2 to 3 hours for 5 doses have given almost uniformly satisfactory results. More recently we have used a single intramuscular injection of 300,000 units in saline with equally good results. We prefer this latter method to the beeswax-oil preparation which has a disadvantage in the vehicle employed. Frequent culture studies are still of the greatest importance in following the course in this field.

Dr. Gold: In relation to the toxicity of combinations of the sulfonamides, attention might be called to the observation that one sulfonamide in a saturated solution will not precipitate

out if another sulfonamide is added to that solution In consequence of this fact, a quantity of sulfonamides composed of 3 *members of the group will make a solution with less hazard of* precipitation than a similar quantity composed of only 1 sulfonamide There is a preparation on the market composed of equal parts of sulfadiazine, sulfamerazine, and sulfathiazole, and there is some indication from observations in man that such a combination provides the therapeutic effects of the sum of the 3, but the hazard of precipitation of crystals in urine is *only that of 1 of the ingredients of the mixture While there* are indications that such a mixture might be advantageous, there is need for more clinical experience to be sure that such a mixture is superior to any one compound alone

Dr Wheeler Dr. Marshall, I wonder if we could have your reaction to the views that have been expressed in regard to the technics and drugs employed in the treatment of genitourinary infections on the urological service

Dr Victor F Marshall In general, I am in agreement with what has already been said Except for gonorrhea and tuberculosis, infections of the urinary tract in the male are usually associated with obstruction or a tumor, or a foreign body. These must be properly treated before the infection can be eradicated. The sulfa drugs seem to be particularly useful in the streptococcal infections and penicillin in the staphylococcal infections There are a few organisms which are still extremely difficult to manage In adult male urology, we have the same trouble with the B pyocyaneus as Dr Glynn has in pediatric practice We have tried streptomycin, and in our limited experience, we have had very little success I remember one patient specifically to whom the drug was given parenterally and also through the nephrostomy following the removal of a stone, and even such intensive streptomycin therapy failed to eliminate the B pyocyaneus The B proteus is another common and very tenacious infection in the urinary tract. It is particularly objectionable because it is a vigorous

ammonia-forming organism which makes the urine highly alkaline and promotes the formation of stone. We are extremely eager to eradicate this organism, but our results with sulfa drugs and penicillin have not been satisfactory, and our limited experience with streptomycin has not been promising.

In relation to the sulfa drugs, it is our experience that smaller doses are necessary in the urinary tract than for infections in any other part of the body. This may be so because the effect is exerted not only through the circulation but through the excretion of the drug in the urine.

In gonorrhea, we no longer have to resort to the old-fashioned treatment of local irrigations with silver and the like. Approximately 90 to 95 per cent of the patients that we see in this clinic with an initial attack of acute gonorrhea are cured either with sulfa or penicillin, sometimes with both drugs. Those that remain uncured are usually cases complicated with stricture or some other form of obstruction.

We have had no experience in the use of streptomycin for tuberculosis of the urinary tract, but there is little doubt that, at the present time, the best treatment is still the removal of the focus when it is possible, following this with sanitorial care.

I might say a word about a few of the popular local measures in urinary infections of the adult male. First, the matter of washing the bladder. The reason we wash the bladder is not to sterilize the inside, but to clean it and get rid of debris which is in the bladder. We carry this out with a mild antiseptic, such as acriflavin, which lends a bacteriostatic quality to the residual urine. We should remember, however, that it is the residual urine which matters, since this indicates obstruction, and the obstruction still remains the chief problem. Next is the matter of prostatic massage. A judicious program of prostatic massage is a valuable adjunct to the treatment of chronic prostatitis. The prostate should be massaged gently for

the purpose of expressing prostatic fluid This promotes drainage The prostate is a honeycomb like organ, and there is nothing to make it drain except the continued formation and flow of prostatic fluid Infection leads to obstruction of the ducts so that drainage is impaired Heat, as usually applied by the sitz bath or diathermy, is sometimes helpful The sulfa drugs and penicillin are quite worthless in chronic prostatitis It is otherwise, however, in acute prostatitis In the latter, local heat, together with sulfa drugs and penicillin, is quite effective in controlling the infection and the patient's symptoms The careless application of prostatic massage entails dangers If you vigorously massage the prostate of a perfectly normal male a few times a week for a few weeks, you are likely to find pus cells in his urine which were not there before

I am in general agreement with the statements that have been made about the various antimicrobial agents used in urinary tract infections Pyridium seems to have a slightly sooth ing action on the genitourinary tract. Exactly how, I do not know Its antiseptic properties are quite weak

I might summarize by saying that penicillin and the sulfa drugs have revolutionized the treatment of gonorrhea In the case of tuberculosis, the removal of the focus when feasible together with general medical care is still the principal form of therapy Local treatments are of value when applied gently and in moderation, but the main principles of other therapy of urinary infections in the male are still the same as in the days before chemotherapy, since obstruction, tumors, and for eign bodies are still the chief problems Chemotherapeutic agents are helpful in avoiding complications in the surgical management of these conditions, but the fundamentals of the surgical problems have not been essentially altered

Dr Cattell Neither Dr Glynn in pediatrics nor Dr Doug las in obstetrics and gynecology seems to lean very heavily on penicillin I wonder why it is not as useful in the patients they see as in those of Dr Marshall in male urology

ammonia forming organism which makes the urine highly alkaline and promotes the formation of stone We are extremely eager to eradicate this organism, but our results with sulfa drugs and penicillin have not been satisfactory, and our limited experience with streptomycin has not been promising

In relation to the sulfa drugs, it is our experience that smaller doses are necessary in the urinary tract than for infections in any other part of the body This may be so because the effect is exerted not only through the circulation but through the excretion of the drug in the urine

In gonorrhea, we no longer have to resort to the old fashioned treatment of local irrigations with silver and the like Approximately 90 to 95 per cent of the patients that we see in this clinic with an initial attack of acute gonorrhea are cured either with sulfa or penicillin, sometimes with both drugs Those that remain uncured are usually cases complicated with stricture or some other form of obstruction

We have had no experience in the use of streptomycin for tuberculosis of the urinary tract, but there is little doubt that at the present time, the best treatment is still the removal of the focus when it is possible, following this with sanitorial care

I might say a word about a few of the popular local measures in urinary infections of the adult male First, the matter of washing the bladder The reason we wash the bladder is not to sterilize the inside, but to clean it and get rid of debris which is in the bladder We carry this out with a mild antiseptic, such as acriflavin which lends a bacteriostatic quality to the residual urine We should remember, however that it is the residual urine which matters, since this indicates obstruction, and the obstruction still remains the chief problem Next is the matter of prostatic massage A judicious program of prostatic massage is a valuable adjunct to the treatment of chronic prostatitis The prostate should be massaged gently for

the purpose of expressing prostatic fluid. This promotes drainage. The prostate is a honeycomb-like organ, and there is nothing to make it drain except the continued formation and flow of prostatic fluid. Infection leads to obstruction of the ducts so that drainage is impaired. Heat, as usually applied by the sitz bath or diathermy, is sometimes helpful. The sulfa drugs and penicillin are quite worthless in chronic prostatitis. It is otherwise, however, in acute prostatitis. In the latter, local heat, together with sulfa drugs and penicillin, is quite effective in controlling the infection and the patient's symptoms. The careless application of prostatic massage entails dangers. If you vigorously massage the prostate of a perfectly normal male a few times a week for a few weeks, you are likely to find pus cells in his urine which were not there before.

I am in general agreement with the statements that have been made about the various antimicrobial agents used in urinary tract infections. Pyridium seems to have a slightly soothing action on the geniturinary tract. Exactly how, I do not know. Its antiseptic properties are quite weak.

I might summarize by saying that penicillin and the sulfa drugs have revolutionized the treatment of gonorrhea. In the case of tuberculosis, the removal of the focus, when feasible, together with general medical care, is still the principal form of therapy. Local treatments are of value when applied gently and in moderation, but the main principles of other therapy of urinary infections in the male are still the same as in the days before chemotherapy, since obstruction, tumors, and foreign bodies are still the chief problems. Chemotherapeutic agents are helpful in avoiding complications in the surgical management of these conditions, but the fundamentals of the surgical problems have not been essentially altered.

Dr. Cattell: Neither Dr. Glynn in pediatrics nor Dr. Douglas in obstetrics and gynecology seems to lean very heavily on penicillin. I wonder why it is not as useful in the patients they see as in those of Dr. Marshall in male urology.

ammonia forming organism which makes the urine highly alkaline and promotes the formation of stone We are extremely eager to eradicate this organism, but our results with sulfa drugs and penicillin have not been satisfactory, and our limited experience with streptomycin has not been promising

In relation to the sulfa drugs it is our experience that smaller doses are necessary in the urinary tract than for infections in any other part of the body This may be so because the effect is exerted not only through the circulation but through the excretion of the drug in the urine

In gonorrhea, we no longer have to resort to the old fashioned treatment of local irrigations with silver and the like Approximately 90 to 95 per cent of the patients that we see in this clinic with an initial attack of acute gonorrhea are cured either with sulfa or penicillin, sometimes with both drugs Those that remain uncured are usually cases complicated with stricture or some other form of obstruction

We have had no experience in the use of streptomycin for tuberculosis of the urinary tract, but there is little doubt that at the present time, the best treatment is still the removal of the focus when it is possible, following this with sanitorial care

I might say a word about a few of the popular local measures in urinary infections of the adult male First the matter of washing the bladder The reason we wash the bladder is not to sterilize the inside, but to clean it and get rid of debris which is in the bladder We carry this out with a mild antiseptic, such as acriflavin, which lends a bacteriostatic quality to the residual urine We should remember, however, that it is the residual urine which matters since this indicates obstruction, and the obstruction still remains the chief problem Next is the matter of prostatic massage A judicious program of prostatic massage is a valuable adjunct to the treatment of chronic prostatitis The prostate should be massaged gently for

Dr Gold Do you ever use any other than sulfadiazine, Dr. Glynn?

Dr Glynn Very seldom

Dr Gold Do you, Dr Douglas?

Dr Douglas I don t use anything else

Dr Cary Eggleston May I ask Dr Marshall what is the experience in the use of sulfadiazine in rather benign mild degrees of chronic prostatic infection? He mentioned chronic prostatism It was not quite clear to me as to the effects which he had observed from sulfadiazine

Dr Marshall Our success with it in chronic prostatitis is almost nil

Dr Gold Dr Marshall have you prescribed a dose of pyridium in the past 6 months?

Dr Marshall I am not sure Maybe once

Dr Eggleston Others do

Dr Marshall The reason I mentioned it is because it is very commonly prescribed throughout the City of New York

Dr Douglas In response to the question on pyridium, the main thing we do is to discontinue it

Dr Gold Are we to gain the impression here that streptomycin does not have much place in urinary tract infections?

Dr Wheeler Dr McDermott, what have you to say about that?

Dr McDermott Streptomycin is effective in urinary infections caused by E coli and other gram negative bacteria which invade the urinary tract, such as Bacillus lactis aerogenes Bacillus proteus, Friedlander s bacillus and in some instances, Bacillus pyocyaneus In uncomplicated cases caused by E. coli, which is the commonest infection of the urinary tract seen by the internist however, I believe sulfadiazine should be used first Streptomycin is of special value in E coli infections complicated by bacteremia or metastatic abscesses arising in urinary tract obstructions.

means of urethral irrigations with weak solutions of silver nitrate and forced fluids

The other condition you speak of is really a very difficult one One of the greatest problems in it is the patient s mental attitude He is extremely worried about it and often has some feeling of guilt connected with it It is doubly hard to deal with both the patient and his infection The infection is often times very obstinate, and one of the commonest reasons for persistent trouble is that the patient has been overtreated Many of these patients who have gotten out of the Army, have had prostatic massage, a large number of sounds passed, and the urethra traumatized with all sorts of solutions and anti septics What we usually do when they first arrive is try to determine whether there is any obstructive element Most of them are young and are likely to have escaped examination for obstructions Usually they will be found in the glands near the meatus and those may harbor the infection We pass an instrument of some kind to determine whether they have any appreciable stricture If all these prove negative and the patients have no marked general symptoms, we usually tell them to take sitz baths and do nothing else We carry them along this way with abundant reassurance during a period of 2 or 3 weeks and see what happens A small number will improve quite markedly Some of these patients who have nothing but a slight morning drop will get well if one can only get them to avoid too much treatment When they are overtreated the discharge increases, and with this their worries increase Then they go for more treatment and before long they are back where they started There are various methods of treating these cases The sulfa drugs are occasionally effective

Dr Gold When you speak of sulfa drugs, Dr Marshall do you mean sulfadiazine?

Dr Marshall Yes sulfadiazine, usually 1 Gm 3 times a day or 0 5 Gm 4 times a day.

Dr Gold Do you ever use any other than sulfadiazine Dr Glynn?

Dr Glynn Very seldom

Dr Gold Do you Dr Douglas?

Dr Douglas I don t use anything else

Dr Cary Eggleston May I ask Dr Marshall what is the experience in the use of sulfadiazine in rather benign mild degrees of chronic prostatic infection? He mentioned chronic prostatism It was not quite clear to me as to the effects which he had observed from sulfadiazine

Dr Marshall Our success with it in chronic prostatitis is almost nil

Dr Gold Dr Marshall have you prescribed a dose of pyridium in the past 6 months?

Dr Marshall I am not sure Maybe once

Dr Eggleston Others do

Dr Marshall The reason I mentioned it is because it is very commonly prescribed throughout the City of New York

Dr Douglas In response to the question on pyridium the main thing we do is to discontinue it

Dr Gold Are we to gain the impression here that streptomycin does not have much place in urinary tract infections?

Dr Wheeler Dr McDermott what have you to say about that?

Dr McDermott Streptomycin is effective in urinary infections caused by E coli and other gram negative bacteria which invade the urinary tract such as Bacillus lactis aerogenes Bacillus proteus Friedlander s bacillus and in some instances Bacillus pyocyaneus In uncomplicated cases caused by E. coli which is the commonest infection of the urinary tract seen by the internist however I believe sulfadiazine should be used first Streptomycin is of special value in E coli infections complicated by bacteremia or metastatic abscesses arising in urinary tract obstructions.

Dr. Modell: Dr. McDermott, when you indicate that you prefer to use sulfadiazine in urinary tract infections in which streptomycin is also effective, what is your reason? Is it because sulfadiazine is more effective, cheaper, or less toxic?

Dr. McDermott: Because sulfadiazine is less toxic; the toxicity of streptomycin is not inconsiderable.

Dr. Ralph R. Tompsett: I should like to mention the possibilities for use of "combined" therapy in those patients with urinary tract infections for which streptomycin is indicated. There is excellent reason for believing that the emergence of resistant strains of organisms during the course of streptomycin therapy may be delayed or prevented by the concurrent administration of another antibacterial agent which also inhibits the organisms. Inasmuch as many of the organisms responsible for urinary tract infections are inhibited by the sulfonamides as well as by streptomycin, these infections would appear to offer an ideal situation for the use of "combined" therapy with the two drugs.

SUMMARY

Dr. Gold: In the conference this afternoon on the treatment of genitourinary infections, several of the problems which arise in this field of therapy were discussed in some detail. There were the special aspects of these diseases encountered in the practice of adult male urology, in obstetrics and gynecology, and in pediatric practice. The topics included gonorrheal urethritis, non-specific urethritis, acute and chronic prostatitis, urinary infections in association with pregnancy, cystitis, pyelitis and pyelonephritis.

Considerable progress has been made in the management of these conditions in recent years. It is attributable not only to the utilization of more potent chemotherapeutic agents, but to the recognition of the fact that structural abnormalities in the genitourinary tract are frequently responsible for the occurrence and persistence of infections, such abnormalities as

congenital anomalies stones, tumors, and obstructions of various kinds These limit the efficacy of chemotherapeutic agents and account for the fact that, even with the most potent agents infections may fail to clear up or may recur after the organisms have been eliminated

Various diagnostic points were touched upon but the most important diagnostic measures which were stressed by all participants are the excretory urogram, the smear, and the culture

The importance of relieving obstructions and promoting free drainage received special emphasis At the same time it was pointed out that local mechanical procedures such as cystoscopy, the passing of sounds the massage of the prostate, and local irrigations are sources of danger they tend to traumatize the tissues and promote infection Massage of the prostrate has generallv fallen into disrepute and while gentle massage is still sometimes necessary to promote drainage it was pointed out that vigorous massage may cause the appearance of pus in the urine of normal men Irrigation of the bladder with antiseptics is no longer regarded as a means of sterilizing the bladder, but only for the purpose of cleansing and removal of debris

The rôle of urinary antiseptics has been better defined The multitude of dyes which color the urine seem to be of little value Several antimicrobial agents used in urinary infections were discussed, namely, pyridium mandelic acid calcium mandelate, methenamine, the sulfonamides penicillin, and streptomycin

In the treatment of gonorrhea sulfadiazine in doses of about 4 Gm per day for a period of about a week, together with an equal dose of sodium bicarbonate yields a very high incidence of cures Penicillin, however, seems to be preferred at the present time In the use of this agent there are various rapid dosage schedules which provide cures in about 95 per cent of the cases such as a total of 200 000 units given by intramuscular injection in divided doses over a period of about 5 hours,